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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 125 702**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 84105585.8

(22) Date of filing: 16.05.84

(51) Int. Cl.³: **C 07 C 91/10**
C 07 C 93/04, C 07 C 93/14
C 07 C 91/14, C 07 C 89/00
C 07 C 47/575, A 61 K 31/13
A 61 K 31/645, A 61 K 31/12
C 07 C 119/10, C 07 C 103/78

(30) Priority: 17.05.83 GB 8313571

(43) Date of publication of application:
21.11.84 Bulletin 84/47

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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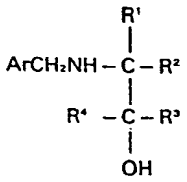
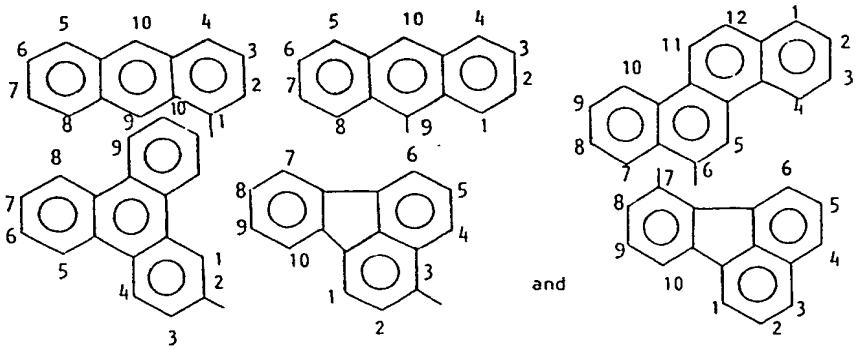
(54) Polycyclic aromatic compounds.

(57) Compounds of the formula (I)



or monomethyl or monoethyl ethers thereof, the compounds including their ethers containing no more than 28 carbon atoms in total, or esters or salts thereof;

wherein Ar is selected from the group comprising:



and

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optionally substituted by one or two substituents which taken together contain not more than four carbon atoms in total and which are the same or different and are selected from halo; cyano; C_{1-3} alkyl or C_{1-3} alkoxy each optionally substituted by hydroxy or C_{1-2} alkoxy; halo substituted C_{1-2} alkyl or C_{1-2} alkoxy; a group $S(O)_nR^5$ wherein n is an integer 0,1 or 2 and R^5 is C_{1-2} alkyl optionally substituted by hydroxy or C_{1-2} alkoxy; or Ar is optionally substituted by a group NR^6R^7 containing not more than 5 carbon atoms wherein R^6 and R^7 are the same or different and each is a C_{1-3} alkyl group or NR^6R^7 forms a five or six membered heterocyclic ring optionally containing one or two additional hetero atoms;

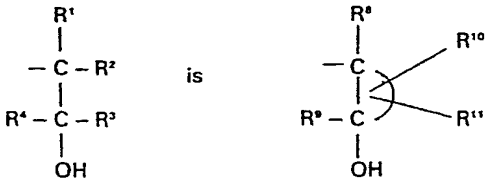
R^1 is C_{1-3} alkyl substituted by hydroxy;

R^2 is hydrogen, C_{1-3} alkyl or hydroxymethyl;

R^3 and R^4 are the same or different and each is hydrogen, methyl or ethyl;

R^1, R^2, R^3 and R^4 taken together containing not more than five carbon atoms;

or the group:



wherein $-\overset{\frown}{C-C}-$ is a five or six membered saturated carbocyclic ring containing two or three hydroxy groups;

R^8 is hydrogen, methyl or hydroxymethyl;

R^9 and R^{10} are the same or different and each is hydrogen or methyl;

R^{11} is hydrogen, hydroxy, methyl or hydroxymethyl;

R^8, R^9, R^{10}, R^{11} and the $-\overset{\frown}{C-C}-$ ring taken together containing less than seven carbon atoms which have biocidal, and particularly antitumour, activity are described as are methods for their preparation, their use in medicine and pharmaceutical formulations containing them.

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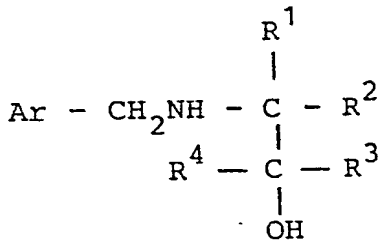
The present invention relates to polycyclic aromatic alkanol derivatives which have been found to have biocidal activity. More specifically the invention concerns aminoalkanol derivatives containing a polycarbocyclic aromatic ring system, methods for the synthesis thereof, pharmaceutical formulations thereof, novel intermediates therefor, pharmaceutical formulations thereof and their use as biocidal agents, particularly antitumour agents.

Gazz. Chim. Ital., 93, 118, (1963) describes the preparation of 2-phenylmethylamino-2-methyl-1,3-propanediol but no antitumour activity is disclosed for this compound. Two analogues of nitracrine (1-nitro-9-((3'-dimethylaminopropyl)amino)acridine) containing 2-amino-2-methyl-1,3-propanediol and tris (hydroxymethyl)methylamine groups are disclosed in Arzneim Forsch Drug Res. 32II,1013,(1982) as having antitumour activity in murine screening systems.

We have now discovered a class of novel polycarbocyclic aromatic alkanol derivatives which have biocidal activity. Accordingly, in a first aspect, the present invention provides a compound of the formula (I):



(I)

or a monomethyl or monoethyl ether thereof, the compound of formula (I) including its ethers containing no more than 2 8 carbon atoms in total, or an ester or salt thereof;

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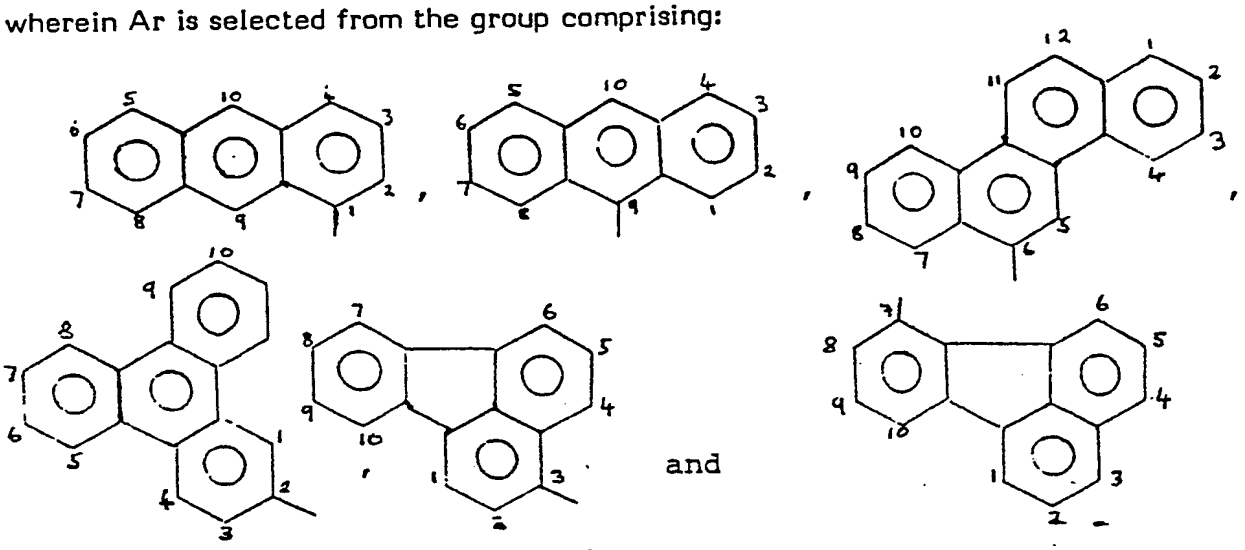
wherein Ar is selected from the group comprising:



and

optionally substituted by one or two substituents which taken together contain not more than four carbon atoms in total and which are the same or different and are selected from halo; cyano; C_{1-3}alkyl or C_{1-3}alkoxy each optionally substituted by hydroxy or C_{1-2}alkoxy; halo substituted C_{1-2}alkyl or C_{1-2}alkoxy; a group $S(O)_nR^5$ wherein n is an integer 0,1 or 2 and R^5 is C_{1-2} alkyl optionally substituted by hydroxy or C_{1-2} alkoxy; or Ar is optionally substituted by a group NR^6R^7 containing not more than 5 carbon atoms wherein R^6 and R^7 are the same or different and each is a C_{1-3} alkyl group or NR^6R^7 forms a five or six membered heterocyclic ring optionally containing one or two additional hetero atoms;

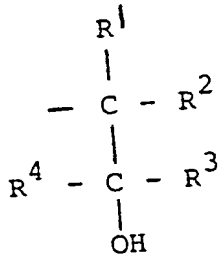
R^1 is C_{1-3} alkyl substituted by hydroxy;

R^2 is hydrogen, C_{1-3} alkyl or hydroxymethyl;

R^3 and R^4 are the same or different and each is hydrogen, methyl or ethyl;

R^1, R^2, R^3 and R^4 taken together containing not more than five carbon atoms;

or the group:



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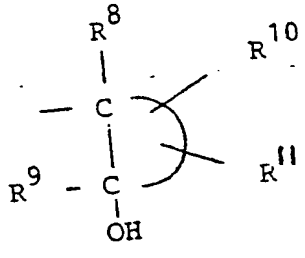


wherein -C-C- is a five or six membered saturated carbocyclic ring containing two or three hydroxy groups;
R^8 is hydrogen, methyl or hydroxymethyl;
R^9 and R^{10} are the same or different and each is hydrogen or methyl;
R^{11} is hydrogen, hydroxy, methyl or hydroxymethyl;

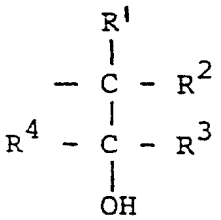
R^8, R^9, R^{10}, R^{11} and the -C-C- ring taken together containing less than seven carbon atoms.

Preferably, when Ar is 1- or 9- anthracenyl, the aromatic ring system is substituted.

Preferably Ar is 6-chrysenyl or 3- or 7-fluoranthenyl.

Particularly suitable substituents for the aromatic ring include C_{1-2} alkyl or C_{1-2} alkoxyl each optionally substituted by chloro, hydroxy or methoxy; or a group $S(O)_nR^5$ or chloro, imidazolyl, morpholino, cyano, bromo. Preferred substituents are chloro, 2-chloroethyl or $OCH_2CH_2R^{12}$ wherein R^{12} is hydrogen, hydroxy or methoxy or a group $S(O)_nCH_3$ wherein n is the integer 0, 1 or 2. The substituents may be attached to any appropriate position on the aromatic ring. Preferably when Ar is substituted, this is by one substituent only.

Suitably



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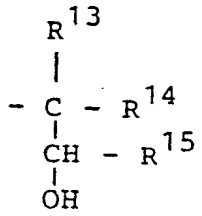

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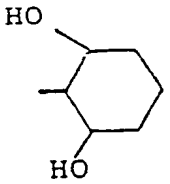
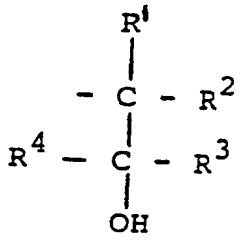


wherein
R^{13} is CH_2OH, $CH(CH_3)OH$ or CH_2CH_2OH,
R^{14} is hydrogen, C_{1-3}alkyl, or CH_2OH
R^{15} is hydrogen or methyl.

Preferably R^{13} is CH_2OH or $CH(CH_3)OH$. Suitably R^{14} is hydrogen, methyl, ethyl or CH_2OH.

Preferably the group:



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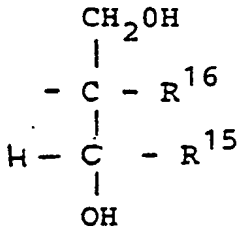


wherein R^{15} is hydrogen or methyl and R^{16} is hydrogen, methyl or ethyl, preferably methyl.

Salts included within the scope of the present invention are those of compounds of formula (I) and ethers and esters thereof.

Esters and non pharmaceutically acceptable salts of the compounds of formula (I) are useful intermediates in the preparation of compounds of the formula (I) and pharmaceutically acceptable salts thereof, and are therefore within the scope of the present invention. Thus, salts of the compounds of the formula (I) useful in the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids such as isethionic, maleic, malonic, succinic, salicyclic, tartaric, lactic, citric, formic, lactobionic and pantothenic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic and naphthalene-2-sulfonic acids; ascorbic and amino acids, such as glycine. Suitable salts include hydrochlorides, methane and ethanesulfonates, lactates, citrates and isethionates. Pharmacologically and pharmaceutically acceptable salts are preferred, particularly those that are soluble in solvents suitable for parenteral administration, for example hydrochlorides, methanesulphonates and isethionates.

Esters of compounds of formula (I) are derived from acids known to those skilled in the art to be suitable for ester formation, and are conveniently those derived from C_{1-6} alkanoic acids, for example acetic acid, propionic acid, n-butyric acid and iso-butyric acid.

The esters may be formed from all, or only some, of the hydroxy groups contained in the compounds of formula (I).

Specific compounds within the scope of formula (I) include, for example

2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((9-Anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((1-Anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Chloro-9-anthracenylmethyl)-amino)-2-methyl-1,3-propanediol,

2-((10-Bromo-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-Methyl-2-((10-methyl-9-anthracenylmethyl)amino)-1,3-propanediol,

2-Methyl-2-((10-methylthio-9-anthracenylmethyl)amino)-1,3-propanediol,

2-((10-(2-Chloroethyl)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Hydroxymethyl)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

10-((1,1-Bis)hydroxymethyl)ethylamino)methyl-9-anthracene-carbonitrile,

2-Methyl-2-((10-methylsulfinyl-9-anthracenylmethyl)amino)-1,3-propanediol,

2-((10-Methoxy-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Bromo-1-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((4,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((4,5-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((2,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((3,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((3-Fluoranthrylmethyl)amino)-2-methyl-1,3-propanediol,

2-Methyl-2-((2-triphenylenylmethyl)amino)-1,3-propanediol,

2-((4-Chloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,
2-((2-Chloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Ethylthio-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-(2-Hydroxyethylthio)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Chloro-9-anthracenylmethyl)amino)-2-hydroxymethyl-1,3-propanediol,

2-((7-Fluoranthenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-(2-Hydroxyethyloxy)-9-anthracenylmethyl)amino-2-methyl-1,3-propanediol,

2-((10-Ethoxy-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((6-Chrysenylmethyl)amino)-2-hydroxymethyl-1,3-propanediol,

2-((6-Chrysenylmethyl)amino)-2-ethyl-1,3-propanediol,

2-Hydroxymethyl-2-((3-fluoranthenylmethyl)amino)-1,3-propanediol,

2-Ethyl-2-((3-fluoranthenylmethyl)amino-1,3-propanediol,

2-((10-chloro-9-anthracenylmethyl)amino)-2-ethyl-1,3-propanediol

2-((3-chloro-9-anthracenylmethyl)amino-2-methyl-1,3-propanediol,

(+-) (2R*, 3S*)-2-((6-chrysenylmethyl)amino)-2-methyl-1,3-butanediol,

2-((2-ethyl-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol and
2-((3-ethyl-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

(+-) (2R*, 3S*)-2-((9-anthracenylmethyl)amino)-2-methyl-1,3-butanediol,

(+-) (2R*, 3R*)-2-(((6-chrysenyl)methyl)amino)-2-methyl-1,3-butanediol,

2-(((6-chrysenyl)methyl)amino)-2-ethoxymethyl-1,3-propanediol,

3-methoxy-2-(((6-chrysenyl)methyl)amino)-2-methyl-1-propanol,

3-methoxy-2(((3-fluoranthenyl)methyl)amino)-2-methyl-1-propanol,

(+-) (2R*, 2S*)-2-(((3-fluoranthenyl)methyl)amino)-2-methyl-1,3-butanediol,

2-ethoxymethyl-2-(((3-fluoranthenyl)methyl)amino)-1,3-propanediol,

2-(((9-anthracenyl)methyl)amino)-2-ethoxymethyl-1,3-propanediol,

2-β-((6-chrysenylmethyl)amino)-1-α,3-α-cyclohexanediol

2-β-((3-fluoranthenylmethyl)amino)-1-α,3-α-cyclohexanediol

2-((6-chrysenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((3-fluoranthenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((6-chrysenylmethyl)amino)-2-methyl-1,4-butanediol

2-((3-fluoranthenylmethyl)amino)-2-methyl-1,4-butanediol

2-(((10-chloro-1-anthracenyl)methyl)amino)-3-methyl-2,5-pentanediol

2-(((10-chloro-1-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

Meso-3-((6-chrysenylmethyl)amino)-2,4-pentanediol

2-((6-chrysenylmethyl)amino)-1,3-propanediol

2-(((12-ethyl-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

2-(((10-(2-methoxyethoxy)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

2-methyl-2-(((10-morpholino-9-anthracenyl)methyl)amino)-1,3-propanediol

2-((9-anthracenylmethyl)amino)-3-methoxy-2-methyl-1-propanol

2-(((12-chloro-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

2-((9-anthracenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((9-anthracenylmethyl)amino)-2-methyl-1,4-butanediol

2-(((10-(1H-imidazol-1-yl)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

2-(4-ethyl-3-fluoranthenyl)methyl)amino)-2-methyl-1,3-propanediol

2-(((12-ethoxy-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

(1α, 2β, 3α)-2-(9-anthracenylmethyl)amino-1,3-cyclohexanediol

2-(((4-chloro-10-hydroxyethoxy)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

(+-) (2R +,/RS +, 4R +) -3-(6-chrysenylmethyl)amino)-3-methyl-2, 5-pentanediol and

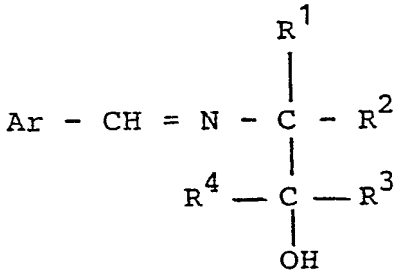
2-methyl-2-(((10-methylsulphonyl-1-9-anthracenyl)methyl)amino) -1,3-propanediol

and salts and esters thereof.

Of these specific examples of compounds of formula (I), the most preferred compounds are 2-((6-chrysenylmethyl)amino)-2-methyl-1,3-propanediol, 2-((3-fluoranthenylmethyl)amino-2-methyl-1,3-propanediol, 2-((10-(2-hydroxyethyloxy)-9-(anthracenylmethyl)amino)-2-methyl-1,3-propanediol.

The compounds of formula (I) and their ethers, esters and salts thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure. Thus the compounds of formula (I) may, for example, be prepared by any of the methods defined below.

1. The reduction of a compound of formula (II):



(II)

wherein R^1 to R^4 are as hereinbefore defined or an appropriately protected derivative thereof, followed by deprotection where appropriate. The conditions and reagents for such a reaction are well known to those skilled in the art and any such conditions/reagents may be employed. The reduction conveniently is carried out by a metal hydride such as lithium aluminium hydride, sodium borohydride or sodium cyanoborohydride, or by catalytic hydrogenation conveniently by hydrogen in the presence of a metal catalyst such as palladium or platinum or equivalent reagents as outlined by J. March, Advanced Organic Chemistry, 2nd ed., pages 819-820, McGraw Hill, New York, 1977. The reduction is suitably carried out with the compound of the formula (II) in solution in an inert solvent or mixture of solvents compatible with the reducing agent at a non-extreme temperature, for example between 0^0 and 80^0C and conveniently at room temperature.

In the case of lithium aluminium hydride and like reagents suitable solvents include ethers (for example tetrahyrofuran, diethylether and dimethoxyethane) optionally in the presence of a hydrocarbon co-solvent (for example toluene, benzene, or hexane).

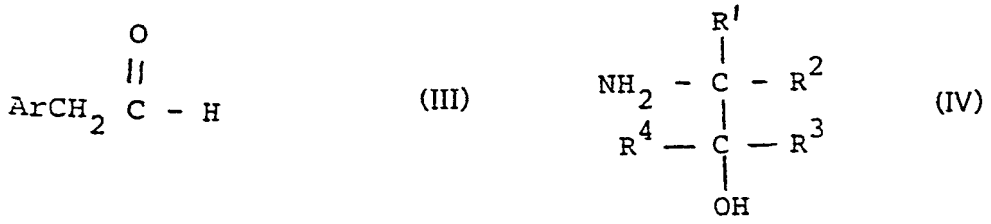
In the case of sodium borohydride and like reagents, suitable solvents include alcohols (for example ethanol, methanol or isopropanol) optionally in the presence of a hydrocarbon co-solvent (for example toluene, benzene or hexane), or an ether co-solvent (for example diethylether or tetrahydrofuran).

In the case of sodium cyanoborohydride and like reagents, suitable solvents include those described for sodium borohydride and the reaction is suitably carried out in the presence of an acid conveniently glacial acetic acid as outlined in, for example, R. Hutchins et al, Organic Preparations and Procedures International, 11, 201, (1979).

In the case of catalylic hydrogenation, suitable solvents include alcohols (for example methanol and ethanol optionally in the presence of a hydrocarbon solvent (for example toluene or benzene) or an ether co-solvent (for example diethyl ether or tetrahydrofuran) in the presence of an acid (for example glacial acetic acid or ethanolic hydrochloric acid) or in glacial acetic acid.

Protected derivatives of compounds of formula (II) are conveniently used when lithium aluminium hydride is employed as the reducing agent. Convenient protecting groups are compatible with the reducing agent utilized and are readily removed under nondestructive conditions; for example benzyl, tetrahydropyranyl, and isopropylidene ethers.

It is often convenient not to isolate the compound of the formula (II) but to react a compound of the formula (III) with a compound of the formula (IV):



(III) (IV)

wherein Ar and R^1 to R^4 are as hereinbefore defined, and reduce the compound of

formula (II) so formed in situ. The reaction of the compounds of the formulae (III) and (IV) is again suitably carried out using conditions and reagents which are well known to those skilled in the art, for example in the presence of an acid, such as a sulfonic acid, i.e. p-toluenesulfonic acid, in an appropriate inert solvent, such as an aromatic hydrocarbon, for example toluene, with azeotropic removal of water followed by treatment with the reducing agent in an appropriate solvent, suitably ethanol or methanol. Alternatively, compounds of formula (II) formed under equilibrium conditions in appropriate solvents are reduced in situ with an appropriate reducing agent, suitably sodium cyanobrohydride. The compound of the formula (III) may be in the form of a protected aldehyde, for example an acetal, which liberates the aldehyde function under the reaction conditions.

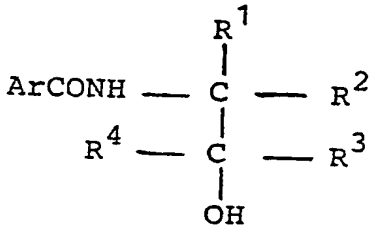
In turn, a compound of formula (III) can be synthesised by reacting the appropriate polycyclic aromatic hydrocarbon with a formylating agent such as that generated by the reaction between $SnCl_4$ and Cl_2CHOCH_3 or equivalent reagents, for example, according to the method A.Reiche et. al. Chem. Ber. 93, 88 (1960), or with other standard formylating reagents/procedures known to the art, for example; the Gatterman-Koch reaction ($CO/HCl/AlCl_3/CuCl$), the Gatterman reaction ($HCN/HCl/ZnCl_2$), and the Vilsmeier reaction ($POCl_3$/PhN(Me)CHO, or $POCl_3/Me_2NCHO$) (J. March, vide supra pages 494-497).

The compounds of the formula (III) may also be prepared from an appropriate polycyclic aromatic hydrocarbon substituted by a suitable functional group such as CH_2OH, $CHBr_2$, N or methyl, and converting this functional group to an aldehyde group by methods well known to those skilled in the art.

Where the polycyclic aromatic ring bears substituents, the compound of formula (III) may be prepared by a variety of methods known in the art of organic chemistry depending on the nature of the substituent on the polycyclic ring. For example if the substituent(s) is a halogen, the starting materials may be prepared by direct treatment of the polycyclic aromatic hydrocarbon with a halogenating agent (e.g. Cl_2, Br_2, or SO_2Cl_2) or indirectly by such routes as the Sandmeyer reaction (D.T. Moury, Chem. Rev. 42, 213 (1948)). If the substituent(s) is alkyl, the polycyclic aromatic hydrocarbon may be reacted with the appropriate reagents under Friedel-Crafts reaction conditions (P.Gore, Chem. Rev. 55 229, (1955)).

The compounds of the formula (IV) also may be prepared by methods known in the art, for example by the reaction of compound $NO_2CH_2R^2$ with an appropriate aldehyde, conveniently acetaldehyde or formaldehyde, (as in B.M.Vanderbilt and H.B. Haas, Ind. Eng. Chem. 32, 34 (1940)) followed by reduction (as outlined in T. March, vide supra 1125-1126) conveniently by hydrogen in the presence of a metal catalyst, for example a platinum containing catalyst, in an appropriate solvent, conveniently glacial acetic acid.

2). The reduction of a compound of the formula (V):



(V)

wherein Ar and R^1 to R^4 are as hereinbefore defined and the hydroxy groups are optionally protected, followed by deprotection of the hydroxy groups where appropriate. The reduction may be carried out by standard reducing agents known for carrying out this type of reduction, for example, a hydride such as lithium aluminium hydride in an inert solvent, such as an ether, i.e. tetrahydrofuran at a non-extreme temperature, for example, at between 0^0 and 100^0C and conveniently at the reflux temperature of the ether.

The compound of the formula (V) may be formed by the reaction of the appropriate acid ArCOOH, or a suitable reactive acid derivative thereof, for example, an acid halide, in an inert solvent with an amine of the formula (IV) in which the hydroxy groups are optionally protected; for example when the compound of the formula (IV) is a diol, by an isopropyledene group. The compound of the formula (V) so formed is suitably reduced in situ and deprotected where appropriate to a compound of the formula (I). The compounds of the formula ArCOOH can be prepared by methods well known to those skilled in the art.

3) The reaction of a compound $ArCH_2L$, wherein Ar is as hereinbefore defined and L is a leaving group, with a compound of the formula (IV) as hereinbefore defined. Suitable leaving groups are those defined by J. March, vide supra pages 683 and 895, and include halogens, such as chlorine and bromine, and sulphonic acid derivatives such as p-toluenesulfonate. The reaction is suitably carried out in an appropriate solvent, such as a dipolar aprotic solvent or alcohol at a non-extreme temperature, for example between 50^{o} and 150^{o} conveniently between 50 and 100^{o}. The compounds of the formula $ArCH_2L$ can be prepared by methods well known to those skilled in the art.

There is therefore provided, as a further aspect of the invention, a method for the preparation of a compound of formula (I) comprising any method known for the preparation of analogous compounds, in particular those methods defined in (1) to (3) hereinabove. In a yet further aspect, the invention provides novel intermediates involved in the preparation of compounds of the formula (I).

The compounds of formula (I) have biocidal activity in that they are toxic to certain living cells that are detrimental to mammals, for example, pathogenic organisms and tumour cells. This toxicity to pathogenic organisms has been demonstrated by activity against viruses (eg., Herpes simplex 1/vero), bacteria (eg., Mycoplasma smegmatis and Streptococcus Pyogenes) fungi (e.g., Candida albicans) protozoa (eg., Eimeria tenella) and helminths (eg., Nippostrongylus brasiliensis). The antitumour activity of compounds of formula (I) has been shown in a number of recognized screens and primarily by the activity against ascitic P388/0 leukaemia. The activity against ascitic tumours, including P388/0, is evidenced by reduction of tumour cell number in mammals, for example mice bearing ascitic tumours, and their consequent increase in survival duration as compared to an untreated tumour-bearing group. Antitumour activity is further evidenced by measurable reduction in the size of certain solid tumours following treatment of mice with the compounds of this invention compared to an untreated tumour-bearing control group. Thus, compounds of formula (I) have been shown to be active against murine tumours, lymphocytic leukaemia P388/0, lymphocytic leukaemia L1210, melanotic melanoma B16, P815 mastocytoma, MDAY/D2 fibrosarcoma, colon 38 adenocarcinoma, M5076 rhabdomyosarcoma, and Lewis lung carcinoma.

Activity in one or more of these tumour tests has been reported to be indicative of antitumour activity in man (A. Goldin et. al in Methods of Cancer Research ed. V.T. DeVita. Jr., and H. Busch, 16 165, Academic Press, N.Y. 1979).

There are sublines of P388/0 which have been made resistant to the following clinically useful agents; cytosine arabinoside, doxorubicin, cyclophosphamide, L-phenylalanine mustard, methotrexate, 5-fluorouracil, actinomycin D, cis-platin, and bis-chloroethylnitrosourea. Compounds of formula (I) show potent activity against those drug-resistant tumours using the test procedure for P388/0 above.

Compounds of formula (I) have also been found to be active against human tumour cells in primary cultures of gastric, pancreatic, mesothelioma, myeloma, and colon cancers. (As used herein "cancer" is to be taken as synonymous with "malignant tumour" or more generally "tumour" unless otherwise noted). This is a procedure in which the prevention of tumour cell colony formation, i.e., tumour cell replication, by a drug has been shown to correlate with clinical antitumour activity in man (D.D. Von Hoff et al, Cancer Chemotherapy and Pharmacology 6, 265 (1980); S. Salmon and D.D. Von Hoff, Seminars in Oncology, 8, 377 (1981).

Compounds of formula (I) which have been found to have antitumour activity intercalate in-vitro with DNA. This property is determined by viscometric methods using the procedure of W.D. Wilson et al, Nucleic Acids Research 4, 2697, (1954), and a log P as calculated by the method of C. Hansch and A. Leo in Substituent Constants for correlation analysis in Chemistry and Biology, John Wiley and Sons, New York 1979, lying in the range between -2 and +2.5.

The invention further provides a method for the treatment of tumours in animals, including mammals and especially humans, which comprises the administration of an effective, non-toxic amount of the compound of formula (I), an ether or ester thereof, or an acid addition salt thereof.

There is further provided as a further, or alternative, aspect of the invention, a compound of formula (I) for use in therapy, for example as an antitumour agent.

The amount of compound of formula (I) required to be effective as a biocidal agent will, of course, vary and is ultimately at the discretion of the medical or veterinary practitioner. The factors to be considered include the condition being treated, the route of administration, the nature of the formulation; the mammal's body weight, surface area, age and general condition; and the particular compound to be

administered. A suitable effective antitumour dose is in the range of about 0.1 to about 120 mg/kg bodyweight, preferably in the range of about 1.5 to 50 mg/kg for example 10 to 30 mg/kg. The total daily dose may be given as a single dose, multiple doses, e.g., two to six times a day or by intravenous infusion for a selected duration. For example, for a 75 kg mammal, the dose range would be about 8 to 9000 mg per day, and a typical dose would be about 2000 mg per day. If discrete multiple doses are indicated, treatment might typically be 500 mg of a compound of formula I given 4 times per day in the form of a tablet, capsule, liquid (e.g, syrup) or injection.

Whilst it is possible for the active compound (defined herein as compound of formula I or ether, ester or salt thereof) to be administered alone as the raw chemical it is preferable to present the active compound in a pharmaceutcal formulation. Formulations of the present invention, for medical use, comprise an active compound together with one or more pharmaceutically acceptable carriers thereof and optionally other therapeutic ingredients. The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present invention therefor, further provides a pharmaceutical formulation comprising a compound of formula (I) (in the form of the free base, ether, ester or a pharmaceutically acceptable acid addition salt thereof) together with a pharmaceutically acceptable carrier therefor.

There is also provided a method for the preparation of a pharmaceutical formulation comprising bringing into association a compound of formula (I) or an ether, ester or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

Whilst the antitumour activity of the compounds of formula (I) is believed to reside in the free base, it is often convenient to administer an acid addition salt of a compound of the formula (I).

The formulations include those suitable for oral, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with a binder , lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, a mixture of the powdered active compound with any suitable carrier.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar for example sucrose to which may also be added any accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallisation of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a conventional carrier such as cocoa butter.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient. Such formulations suitably comprise a solution of a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula that is isotonic with the blood of the recipient. Thus, such formulations may conveniently contain distilled water, 5% dextrose in

distilled water or saline and a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) that has an appropriate solubility in these solvents, for example the isethionate and methane sulphonate salts and preferably the latter.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

The following Examples are provided by the way of illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius.

General Comments

All solvents were reagent grade and used without further purification with the following exceptions. THF was dried by distillation from Na/K alloy under nitrogen (N_2) and used immediately. Toluene ($PhCH_3$) was distilled from CaH_2 under N_2 and stored over 3A molecular sieves. Chemicals used were reagent grade and used without purification unless noted. The full name and address of the suppliers of the reagents and chemicals is given when first cited. After this, an abbreviated name is used.

Preparative HPLC was carried out on a Waters Prep LC/System 500A machine using two 500 g silica gel (SiO_2) cartridges unless otherwise noted. Plugs of SiO_2 used for purifications were "flash chromatography" silica gel (E. Merck, silica gel 60, 230-400 mesh). An appropriate volume sintered glass funnel was filled approximately 3/4 full with the SiO_2 and packed evenly by tapping the outside of the funnel. A peice of filter paper was then placed on top of the SiO_2 and a solution of the material to be purified applied evenly on the top. Gentle suction through a filter flask moved the eluting solvent through the plug rapidly. The appropriate size fractions were combined as needed and further manipulated.

Satisfactory elemental analyses were obtained for all exemplified compounds of the formula (I). Where elemental analyses were performed on the intermediates or starting materials, those elements analysed for are indicated eg (C, H, N) or (C, H,

Cl) etc. In all of the abovementioned analyses, the experimentally determined values were within ± 0.4% of the calculated values.

Preparation of Starting Materials

A. 6-Chrysenecarbaldehyde

To a 5 L 3-neck flask equipped with overhead mechanical stirrer, thermometer, condenser, and nitrogen line was added chrysene (Eastman Kodak Co., Rochester, N.Y. 14650, 100 g, 0.438 mole) and o-dichlorobenzene (2500 mL). The liquid was warmed until all the large chunks of solid dissolved (80°) and then cooled quickly to give finely divided crystals. After further cooling with a salt-ice bath to 5°, $SnCl_4$ (Aldrich Chemical Co., Milwaukee, Wis. 53201, 98%, 228.2 g, 0.876 mole, 102.4 mL), was added in one portion. No temperature change occurred. Keeping the pot temperature below 5° α, α-dichloromethyl methyl ether (Aldrich, 70.48 g, 0.613 mole, 55.45 mL) was added dropwise over 1 hour. The resulting suspension was warmed slowly to 40° over 4 hours and further stirred for 16 hours. Considerable HCl gas evolution occurred during the warming and the early part of the reaction at 40°. The reaction was then cooled to 10° and hydrolysed by careful addition of 1 L of cold H_2O. After 4 hours the layers were separated and the organic layer filtered, dried with anhydrous Na_2SO_4 (Mallinckrodt Co., St. Louis, Mo., 100 g) and filtered again. The clear yellow solution was split into 2 portions and passed through 500 g plugs of "flash chromatography" silica gel (E.Merk, silica gel 60, 230-400 mesh) using toluene as the eluting solvent with 500 mL fractions. This separated unreacted chrysene (3 g) from the aldehyde and a more polar product. Fractions containing the aldehyde were combined and the toluene removed. Crystals formed during this process and were removed periodically by filtration. After drying in a vacuum oven (at 60°) final yield of 6-chrysenecarbaldehyde was 89.46 g (79.7%) mp = 167-196°.

Example B

10-Methylthio-9-anthracenecarbaldehyde

The procedure of V. Rogovik et al., Zh. Org. Khim. 3, 1315 (1969) was modified in the following way: A 2L 3-neck flask fitted with stirring bar, condenser, additional

funnel, thermometer, N_2 inlet, and bubbler was charged with 10-chloro-9-anthracenecarbaldehyde (Aldrich, 28.0 g, 0.116 mol), and DMF (Aldrich, 1 L). The solid dissolved when the reaction mixture was warmed to 60°. The addition funnel was filled with a solution of Na_2S (Mallinckrodt, 28 g, 0.116 mol) in 30 mL of H_2O. This solution was added rapidly to the flask causing a considerable amount of spattering as the purple thiolate formed. The reaction mixture was stirred at 65° for 45 minutes, then cooled to 30° (ice bath). CH_3I (Aldrich, 27.36 g, 0.193 mol) was then added to the flask dropwise over 5 minutes. The colour of the solution changed from deep purple to yellow after 3 hr. After 15 minutes, 1 L of H_2O was added to the reaction mixture. The yellow solid that formed was collected by filtration, dissolved in hot toluene, (500 mL) dried ($MgSO_4$), and filtered through Celite (Trade Mark). Most of the volume of toluene was removed and the resultant oil swirled with hexane (200 mL) to give a bright yellow solid. The material was dried at 50° affording 25.04 g (86%) of 10-methylthio-9-anthracenecarbaldehyde mp 98.5-99°, (C,H,S).

Example C

10-(2-Chloroethyl)-9-anthracenecarbaldehyde

Using the Vilsmeier procedure (L.F. Fieser, Org. Syn. Coll. Vol III, 98 (1955)), 9-vinylanthracene (Aldrich) gave 10-(2-chloroethyl)-9-anthracenecarbaldehyde mp 158-159°, ($PhCH_3/CH_3OH$), (C, H, Cl).

Example D

A. 1,10-Dichloro-9-anthracenecarbaldehyde and 4, 10-Dichloro-9-anthracene-carbaldehyde

Using the procedure of V.I. Rogovik et al., Zh. Org. Khim 3, 1315 (1967), 1-chloroanthraquinone (Aldrich) gave a mixture of 1,10- and 4,10-dichloro-9-anthracenecarbaldehydes. These compounds were separated by preparative HPLC using toluene as the eluting solvent to give 3.05 g (14%) of 1, 10-dichloro-9-anthracenecarbaldehyde mp 180.5-183°, (R_f = 0.64, SiO_2, $PhCH_3$), (C,H,Cl), and 0.59 g (3%) of 4,10-dichloro-9-anthracenecarbaldehyde mp 167-170°, (R_f = 0.57, SiO_2, $PhCH_3$), (C, H, Cl).

Example E

A. 10-Bromo-9-anthracenecarbaldehyde

This material was made from 9,10-dibromoanthracene (Eastman 20 g, 60 mmol) modifying the procedure of R. Kuhn an H. Fischer, Chem. Ber. 94, 3060 (1961). In this procedure, the reaction mixture was cooled to -78° before the nBuLi was added. The resulting mixture was warmed to RT over 1 hr and then refluxed until the crystalline starting material disappeared. The mixture was then cooled to -78° again before the DMF was added (in one portion). The flask was warmed to RT and then quenched with 1M HBr (200 mL). The two-phase system was then extracted with CH_2Cl_2 (3 x 500 mL). The extracts were combined, dried ($MgSO_4$), filtered, and the solvent removed to give the crude material. This was purified by preparative HPLC using toluene as the eluting solvent. After the solvent was removed 13.06 g (76%) of 10-bromo-9-anthracenecarbaldehyde mp 215-216.5°, (lit, mp 218°, P. Kuhn and H. Fischer, Chem. Ber. 94, 3060 (1961)), (C, H, Br) was obtained.

Example F

4,5-Dichloro-9-anthracenecarbaldehyde

1,8-Dichloroanthracene prepared by the method of H.O. House et al. (J. Org. Chem. 38, 1167 (1973)), was formylated by the method outlined in A (except that CH_2Cl_2 was used as the reaction solvent) to give 4,5-dichloro-9-anthracenecarbaldehyde mp 218-220°, ($PhCH_3/CH_3OH$), (C, H, Cl), (lit. 224-226°, E.L. Stogryn, J. Med. Chem. 17, 563 (1974)).

Example G

Formylation of Fluoranthene

Fluoranthene (Aldrich, 100 g, 0.49 mol) was formylated according to the procedure outlined in A (except that CH_2Cl_2 was used as the reaction solvent). The crude material was passed through a 1000 g plug of SiO_2 using toluene as the eluting solvent (3 L). The fractions containing the mixtures of aldehydes were combined

and the solvent removed giving 115 g of crude yellow oil. This material was dissolved in 500 mL of CH_2Cl_2 and diluted to 1 L with hexane. A yellow precipitate formed and this was isolated by filtration. The solid (which is 3-fluoranthene-carbaldehyde) was crystallized from CH_2Cl_2/hexane and dried at 50° to give 45.7 g of pure material. The filtrate was added to the remaining impure mixture and the solvent removed. The remainder of the material was chromatographed on a 1000 g plug of SiO_2 using $PhCH_3$ as eluting solvent. From this mixture, three aldehydes (including more of the 3- isomer) were obtained. The total amounts isolated, identity, and TLC behaviour ($SiO_2/PhCH_3$) of these aldehydes are shown below.

I. 3-Fluoranthenecarbaldehyde 68.73 g (61%) mp 103-104.5°, (R_f = 0.27, (C, H), (lit. mp 98-99°, N. Campbell and N.H. Wilson, Chem. and Ind., 1114, (1970).

II. 7-Fluoranthenecarbaldehyde 2.10 g (2%) mp 139-141°, (C, H), R_f = 0.38

III 8-Fluoranthenecarbaldehyde 24.8 g (22%) mp 91.5-93°, (C, H), (R_f = 0.19).

Example H

4-Chloro-9-anthracenecarbaldehyde

1-Chloroanthracene prepared from 1-chloroanthraquinone (Aldrich) by the method of H.O. House et. al. (J. Org. Chem. 38, 1167, (1973)) was formylated by the procedure outlined in A (except that CH_2Cl_2 was used as the reaction solvent to give 4-chloro-9-anthracenecarbaldehyde mp 129-131°, ($PhCH_3/CH_3OH$), (C, H, Cl).

Example I

10-Methylsulfinyl-9-anthracenecarbaldehyde

A 1L round bottom flask fitted with addition funnel and stirring bar was charged with 10-methylthio-9-anthracenecarbaldehyde (example B, 12.0 g, 48 mmol) and 450 mL of CH_2Cl_2. The resulting solution was cooled to 5° with an ice bath. A solution of MCPBA (Aldrich (85%), 9.64 g, 48 mmol) in 350 mL of CH_2Cl_2 was then added dropwise to the flask over 1 hr. The reaction mixture was allowed to warm

to RT over 1 hr and then was washed with 5% $NaHCO_3$ solution (2 x 500 mL), dried (Na_2SO4), filtered, concentrated to 500 mL, and passed through SiO_2 (250 g) using toluene (5 L) as the eluting solvent. The desired material was then eluted from the SiO_2 using EtOAc (2 L) as the eluting solvent. The solvent volume was reduced to 100 mL and then filtered to 700 mL with hexane. The resulting yellow solid was filtered and dried at 50° to give 11.98 g (94%) of 10-methylsulfinyl-9-anthracenecarbaldehyde mp 182-184°, (C, H, S).

Example J

2-Triphenylenecarbaldehyde

Using the formylation procedure described in A (except that the reaction temperature was 85°), triphenylene (Aldrich) gave 2-triphenylenencarbaldehyde mp 160-161.5°, (CH_2Cl_2/CH_3OH), (C, H).

Example K

10-Methoxy-9-anthracenecarbaldehyde

A 2 L round bottom flask fitted with distilling head, thermometer, and condenser was charged with 15-crown-5 (Aldrich, 25.89 g, 0.118 mol), $NaOCH_3$ (Aldrich, 7.62 g, 0.141 mol), and CH_3OH (50 mL). After 5 minutes 10-chloro-9-anthracenecarbaldehyde (Aldrich 28.4 g, 0.118 mol) and 900 mL of dry toluene were added to the clear colourless solution. The solvent was distilled off until the head temperature reached 108° (300 mL). Additional dry toluene was added to give a total of 1 L volume. The reaction mixture was refluxed for 4 hr, cooled and poured onto a large plug of SiO_2 (1000 g) in a sintered glass funnel. The crude product was chromatographed using toluene as eluent (5 L). The fractions (250 mL) containing the product were combined (≈3 L) and the solvent volume reduced to 500 mL. The shiny golden crystals which formed were filtered to give, after drying at 50°, 15.6 g of material. The volume of the filtrate was reduced to 200 mL and more material fell out of solution and this was filtered and dried to give 6.1 g of additional material. The two crops were combined to give 22.51 g (81%) of 10-methoxy-9-anthracenecarbaldehyde which was used without further purification. Recrystallization gave analytically pure material mp 164.5-166.5°, ($PhCH_3$), (C, H), (lit. mp 165°, J.B. Conant and M. Bramann, J. Amer. Chem. Soc. 50, 2305 (1928)).

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Example L

10-Formyl-9-anthracenecarbonitrile

A 25 mL 2-neck round bottom flask fitted with thermometer, condenser, N_2 inlet and bubbler, and stirring bar was charged with 10-chloro-9-anthraldehyde (Aldrich, 5g, 21 mmol), CuCN (Fisher Scientific Company, 711 Forges Ave., Pittsburgh, PA, 15219, 2.14 g, 24 mmol), N-methyl-pyrrolidinone (100 mL), DMF (15 mL), and bis (triphenylphosphine) palladium dichloride (Fluka, 0.08 g, 01. mmol). The mixture was warmed to 170° and stirred 15 hr under N_2. After 1.5 hr, the mixture became homogenous. The reaction was cooled to 70° and poured into a solution composed of 16 g of $FeCl_3.6H_2O$, (Mallinckrodt), 70 mL of 1.0 M HCl and 400 mL H_2O. The resulting mixture was stirred at 60-70° for 1 hr, filtered and a crude orange solid isolated. This material was dissolved in 1 L of hot toluene and passed through a small plug (100 g) of SiO_2. The filtrate was then concentrated to 75 mL and diluted with hexane (200 mL). The orange solid which formed was collected by filtration and dried to give 3.17 g (68%) of 10-formyl-9-anthracenecarbonitrile mp 270-275°, (C, H, N).

Example M

9,10-Dihydro-9,10-dioxo-1-anthracenecarboxylic acid

Benzanthrone (Aldrich, Technical grade) was purified by chromatography on a plug of SiO_2 with $PhCH_3$ as eluent (83% recovery). mp. 172-172.5° (lit. mp. 170-171°, O. Bally and R. Scholl, Ber. 44, 1656 (1911)).

The purified benzanthrone (63.7 g, 0.277 mol) was dissolved in 15 mL of glacial HOAc at 90° and stirred with a mechanical stirrer. After cooling to 80° solid CrO_3 (Mallinckrodt 200 g, 2 mol) was added in ≈5 g portions over about 4 hr. The exothermic reaction maintained the mixture at ≈80° during this time and CO_2 was evolved. After CO_2 evolution ceased and the reaction temperature fell, the heating mantle was reapplied and the reaction stirred overnight. H_2O (1.5 L) was then added to the dark-green solution. The reaction was then filtered to give a deep brown solid which was washed with Ch_3OH (200 mL) until the washings were

colourless. The resulting solid was dissolved 2 L of hot methoxyethanol and filtered through Celite (Trade Mark) to remove a black solid residue. The volume of the solution was reduced to ≈75 mL (some solid formed) and diluted with 100 mL CH_3OH to give the product. This material was filtered to give 32.0 g (46%) of golden brown 9,10-dihydro-9,10-dioxo-1-anthracenecarboxylic acid mp 287-289°, (C,H), (lit. mp 293-294°, Chemistry of Carbon Compounds IIIb, edited by E.H. Rodd, 1419 (1956), Elsevier, New York.

1-Anthracenecarboxylic acid

To a 5 L 3-neck flask fitted with condenser, thermometer, and overhead stirrer was added 9, 10-dihydro-9,10-dioxo-1-anthracenecarboxylic acid (90 g, 0.357 mol), zinc dust (Mallinckrodt, 250 g, 3.82 mol), $CuSO_4.5H_2O$ (Mallinckrodt, 5g), and 28% NH_4OH (Mallinckrodt, 2500 mL). The mixture was heated slowly until a dark-red solution occurred as the temperature reached 85°. After 3.5 hr the colour of the solution faded to yellow. The reaction was heated an additional 1 hr, and then cooled and the excess zinc filtered. The filter cake was washed with more NH_4OH (100 mL) and then discarded. The filtrate was carefully acidified to pH 1 with conc. HCl added in portions over 1 hr affording a light-green precipitate which was separated by filtration. The solid was washed with H_2O (200 mL) and then recrystallized once from methoxyethanol/H_2O (with a small amount of HCl) filtered, and dried at 75° to give 65 g (82%) of 1-anthracenecarboxylic acid mp 249-250°, (C, H), (lit. mp 245°, Chemistry of Carbon Compounds IIIb, edited by E.H. Rodd, 1373 (1956), Elsevier, New York).

(1-Anthryl)methanol

To a 500 mL 2-neck flask equipped with condenser, addition funnel with N_2 inlet, and stirring bar was added 1-anthracenecarboxylic acid (6.88 g, 31 mmol) and dry THF (250 mL). To the addition funnel, was added a 1M solution of BH_3 in THF (Aldrich, 50 mL, 50 mmol) via a cannula. The BH_3 solution was added over 1 hr and the solution stirred overnight at RT. CH_3OH was then added until H_2 evolution ceased. H_2O (5 mL) and then 1N HCl (5 mL) was added to the flask. The solvents were removed and then toluene (100 ml) added to the flask. The toluene was then also removed. The resulting solid was recyrstallized from EtOAc/hexane to give 4.3 g (67%) of (1-anthryl)-methanol mp 124-125°, (C,H), lit 124-125°, S. Akiyama et al., Bull.Chem. Soc. Jap. 35 (1962)).

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1-Anthracenecarbaldehyde

To a 2 L round bottom flask equipped with condenser and magnetic stirring bar was added (1-anthryl)methanol (21.0 g, 0.10 mol, CH_2Cl_2 (1200 mL) and pyridinium chlorochromate (PCC) (Aldrich, 32.33 g, 0.15 mol). The mixture was then refluxed for 5 hr. The reaction was cooled and then filtered through a 400 g plug of silica gel using toluene as eluting solvent. The first 1 L of solution was collected and concentrated to give 16 g of crude product. This material was purified by preparative HPLC using $PhCH_3$ as eluting solvent. The solvent was removed and the pure material recrystallized from $PhCH_3$/hexane to give 14.0g (67%) of 1-anthracenecarbaldehyde mp 130-131.5°, (C,H), (lit. mp 126.5-127.5°, P.H. Gore J. Chem. Soc. 1616 (1959)).

Example N

(10-Bromo-1-anthryl)methanol

10-Bromo-1-anthracenecarboxylic acid, made from 1-anthracenecarboxylic acid (example M) by the procedure of E. Barnett, J.W. Cook, and H.H. Grainger, Ber. 57 B, 1775 (1924), was reduced with BH_3 in THF by the procedure outlined in 18C to give (10-bromo-1-anthryl)methanol mp 125-127°, (EtOAc/hexane), (C, H, Br).

10-Bromo-1-anthracenecarbaldehyde

Using the procedure outlined in example M oxidation of (10-bromo-1-anthryl)-methanol with PCC gave 10-bromo-1-anthracenecarbaldehyde mp 134.5-135.5°, ($PhCH_3$/hexane), (C, H, Br).

Example O

2-Chloro-9-anthracenecarbaldehyde and 3-chloro-9-anthracenecarbaldehyde

2-Chloroanthracene prepared from 2-chloroanthraquinone (Aldrich) by the method of H.O. House et al. (J. Org. Chem. 38, 1167 (1973)) was formylated by the procedure outlined in A (except that CH_2Cl_2 was used as the reaction solvent) to give a (4:1) mixture of 2-chloro and 3-chloro-9-anthracenecarbaldehydes (87%). Trituration of the material with CH_3OH gave preferential crystallization of 2-

chloro-9-anthracenecarbaldehyde which after further crystallization ($PhCH_3$/hexane) gave the pure 2-chloro isomer mp 149-150° (C, H, Cl) (lit. 148-150°, British Patent 1,149,557). The filtrate (R_f = 0.48, SiO_2, $PhCH_3$) from the CH_3OH trituration was further purified by preparative HPLC to give pure 3-chloro-9-anthraldehyde mp. 122-123.5°, ($PhCH_3$/hexane), (C,H,Cl), (Rf = 0.48, SiO_2, $PhCH_3$).

Example P

10-Ethylthio-9-anthracenecarbaldehyde

Using the procedure described in Example B 10-chloro-9-anthracenecarbaldehyde (Aldrich) and ethyl iodide (Fisher) gave an oil which solidified to give 10-ethylthio-9-anthracenecarbaldehyde mp 74-75.5° (C, H, S).

Example Q

10-((2-Hydroxyethyl)thio)-9-anthracenecarbaldehyde

Using the procedure described in example B (except that the alkylation reaction was run for 1 hr at 65°), 10-chloro-9-anthracenecarbaldehyde (Aldrich), and 2-iodoethanol (Aldrich) gave 10-((2-hydroxyethyl)thio-9-anthracenecarbaldehyde mp 103-104°, ($PhCH_3$/hexane), (C, H, S).

Example R

2,10-Dichloroanthracenecarbaldehyde and 3,10-dichloro-9-anthracene carbaldehyde

Using the procedure of V.I. Rogovik et al. (Zh. Org. Khim. 3, 1315 (1967)) 2-chloroanthraquinone (Aldrich) gave a mixture (≃1:1) of 2,10- and 3,10-dichloroanthracenecarbaldehydes (68%). A portion of the mixture was separated by preparative HPLC using the shave/recycle technique to give 2,10-dichloro-9-anthracenecarbaldehyde mp 175.5-176.5°, ($PhCH_3$), (C, H, Cl), and 3-10-dichloro-9-anthracenecarbaldehyde mp 173.5-175°, ($PhCH_3$), (C, H, Cl). The remainder of the material was used as a mixture.

Example S

10-Ethoxy-9-anthracenecarbaldehyde

Using the procedure outlined in example K, except that NaOEt (Aldrich) EtOH was used instead of $NaOCH_3/CH_3OH$, 10-chloro-9-anthraldehyde (Aldrich) gave 10-ethoxy-9-anthracenecarbaldehyde mp 88-90°, (CH_2Cl_2/hexane (C,H).

Example T

10-(2-hydroxethyloxy)-9-anthracenecarbaldehyde

A 3 L 2-neck flask fitted with thermometer, condenser, stirring bar, N_2 line and bubbler was charged with KOtBu (MCB Manufacturing Chemists. Inc., 2909 Highland Ave, Cincinnati, OH, 45212, 25 g, 0.22 mol), ethyleneglycol (1500 ml) and 10-chloro-9-anthraldehyde (Aldrich, 50 g, 0.207 mol). The mixture was stirred at 100° for 1.5 h. An additional 5 g (45 mmol) of KOtBu was added and the stirring continued for an additional 0.5 h. The reaction mixture was cooled and poured into 1500mL of cold H_2O, stirred for 10 minutes before the precipitate was collected by filtration. The yellow solid was dissolved in 1 L of CH_2Cl_2 and passed through a 100 g plug of SiO_2 using CH_2Cl_2 (9.L). The CH_2Cl_2 was discarded and the desired material eluted with EtOAC (12 L). The appropriate fractions were combined and the solvent removed to give after drying at 50° 10-(2-hydroxyethyloxy)-9-anthracenecarbaldehyde 28.82 g (53%), mp 142-144°, (CH_2Cl_2/hexane), (C,H).

Example U

10-Methylsulfonyl-9-anthracenecarbaldehyde

10-Methylthio-9-anthracenecarbaldehyde (4.50 g, 17.83 mmol) was dissolved in CH_2Cl_2 (100 ml) and cooled to 0° in an ice bath. To the magnetically stirred solution was added dropwise over 15 minutes a solution of m-chloroperbenzoic acid (Aldrich, 85% technical grade, 7.08 g 35.76 mmol) in 250 ml of CH_2Cl_2. The ice bath was removed and the clear solution stirred for 2 h. The solution was then washed sequentially with 10% $Na_2S_2O_3$ solution (500 ml) and satd. Na_2CO_3 solution (2 x 100 ml). The solvent was removed and the crude material passed through a small plug of silica gel (200 ml) in a sintered glass funnel using CH_2Cl_2 as the eluting solvent (500 ml). The solvent was removed to give the crude product which was recrystallized from CH_2Cl_2/EtOH to give 10-methylsulfonyl-9-anthracenecarbaldehyde mp 216-217° (C,H,S).

Example V

10-(2-Methoxyethoxy)-9-anthracenecarbaldehyde

KOtBu (MCB ManufacturingChemists, Inc. 18.2 g, 0.162 mole) in methoxyethanol (1000 ml) was treated with 10-chloro-9-orthraldehyde (Aldrich, 25 g, 0.104 mole) and heated at reflux for 2 h. The cooled reaction mixture was diluted with H_2O (5 L) and the resulting oil stirred for 2 h until solidification occurred. The filtered solid was chromatographed on a plug of SiO_2 (500 g) using CH_2Cl_2 as the eluting solvent to afford 26.9 g (92%) of 10-(2methoxyethoxy)-8-anthracenecarboxaldehyde mp 87-88°, (C,N), (CH_2Cl_2/hexane), (Rf = 0.16, SiO_2, CH_2Cl_2).

Example W

10-Morpholino-9-anthracenecarbaldehyde

10-Chloro-9-anthracene carboxaldehyde (Aldrich, 25 g, 0.104 mole) in morpholine (MCB, practical, 500 ml) was heated at 55° under N_2 for 17 h. The reaction mixture was poured into H_2O (2 L). The filtered precipitate was chromatographed on a plug of SiO_2 (1 kg) using toluene (4 L) as the initial eluting solvent to remove starting material and byproducts. The orange product band was then eluted with CH_2Cl_2 (2 L) to yield 10.58 g (35%) of 10-morpholino-9-anthracenecarboxaldehyde mp 182-184° softens 175°), (C,H,N), (Rf = 0.16, SiO_2, CH_2Cl_2).

Example X

12-chloro-6-chrysenecarbaldehyde

6-Chlorochrysene (Cambridge Chemical. 70 g 0.266 mole) was formylated according to the procedure outlined in example 1A, except that CH_2Cl_2 (2500 ml) was used as the reaction solvent. Chromatography on a plug of SiO_2 (1 kg) using EtOAc as the eluting solvent afforded 19.1 g (25%) of 12-chloro-6-chrysenecarbaldehyde mp 255-257°, (EtOAc), (Rf = 0.42, SiO_2, toluene).

Example Y

10-(Imidazol-1-yl)-9-anthracencarbaldehyde

A solution of 10-chloro-9-anthraldehyde (Aldrich, 15 g, 0.062 mole), imidazole (Aldrich, 10.2 g 0.15 mole), and DMF (300 ml) at 55° was treated with KOtBu

(MCB, 7.9 g, 0.07 mole) and stirred for 30 minutes. The reaction mixture was poured into 0.1M NAOH (1500 ml). The filtered precipitate was chromatographed on a plug of SiO_2 (500 g) using CH_2Cl_2 (3 L) as the initial eluting solvent to remove starting material and byproducts. The yellow product band was then eluted with EtOAc (2 L) to yield 12.29 g (73%) of 10-(imidazol-1-yl)-9-anthracenecarbaldehyde mp 194-196°, (C,H,N), (EtOAc), (Rf = 0.38, SiO_2, EtOAc).

Example Z

2-Ethylanthracene

To a 5 L 3-neck flask fitted with condenser, thermometer, and overhead stirrer was added 2-ethylanthraquinone (Aldrich, 120g, 0.51 mol), Zn dust (Mallinckrodt, 300 g, 4.59 mol), $CaSO_4.5\ H_2O$ (Mallinckrodt, 3.0 g), and 28% NH_4OH (Mallinckrodt, 2800 mL). The temperature was increased until the initial dark red colour had faded (about 6 h). The reaction mixture was then filtered. The filtrate was extracted with EtOAc, and the zinc solid also extracted with EtOAc. The EtOAc solutions were combined and the solvent removed. The residue was refluxed with a mixture of con HCl (10 mL) in n-PrOH (1200 mL) for 2 h. Upon cooling, a solid precipitated which was filtered, washed with abs. EtOH (100 mL) and dried togive 40 g (38%) of 2-ethylanthracene mp, C,H.

2- and 3-Ethylanthracene-9-carbaldehyde

2-Ethylanthracene (40 g, 0.194 mol) was formylated according to the procedure outlined in example A, except that CH_2Cl_2 (500 mL) was used as the reaction solvent. Chromatography over a plug of SiO_2 with $PhCH_3$ as the eluting solvent gave 43.68 g (96%) of a mixture of 2- and 3-ethyl-anthracene-9-carbaldehyde.

Example AA

3,5-Diphenyl-7a(7H)-ethoxymethyl-1H,3H,5H-oxazolo(3,4-c)oxazole

A mechanically stirred 60% dispersion of NaH in mineral oil (Alfa-Ventron, 34.0 g, 0.85 mol) was washed with dry hexane to remove the oil and suspended in dry DMF (300 mL). To the mixture was added a solution of 3,5-diphenyl-1H,3H,5H-

oxazolo(3,4-c)oxazole-7a(7H)-methanol (208.2 g, 0.7 mol, prepared by the method of J. Pierce et al JACS 73 2595 (1951)) in dry DMF (300 mL) keeping the reaction mixture between 30-35°. The salt suspension was stirred at RT for 60 min, diluted with dry DMF (200 mL) to facilitate stirring, cooled, then treated with ethyl iodide (Aldrich, excess) at such a rate that the reaction temperature was between 20-35°. The mixture was stirred at RT for 2 h, then cautiously treated with absolute EtOH (30 mL). The resulting mixture was diluted with Et_2O (2.5 L) and the resulting solids removed by filtration. The solvent was then removed using a rotary evaporator to give 229.5 g of a yellow oil containing both starting material and desired product. A solution of the oil in chloroform was mixed with SiO_2 (200 g) and the solvent removed. The solid was then added to a column of SiO_2 (800 g). Elution with the EtOAc/hexane (1:3.5) gave 139.7 g (61.3%) of 3,5-diphenyl-7a(7H)-ethoxymethyl-1H,3H,5H-oxazolo(3,4-c)oxazole. An analytical sample was obtained by recrystallization from hexane, mp of 83.5-85°, (C,H,N). The bulk of the material was used without further purification.

2-Amino-2-ethoxymethoxy-1,3-propanediol hydrochloride1\4H_2O

3,5-Diphenyl-7a(7H)-ethoxymethyl-1H,3H,5H-oxazolo(3,4-c)oxazole (136 g, 0.42 mol) was dissolved in 6 N HCl (400 mL) and the resulting solution stirred 1.5 h at RT. After extraction with Et_2O (2x200 mL) to remove benzaldehyde, the aqueous solution was concentrated on a rotary evaporator to give a colourless oil. This was cooled in an ice bath to facilitate cystallization. The solid which formed was slurried with cold CH_3CN, filtered, then washed with Et_2O and dried in a vacuum oven at RT to give 71 g (89%) of 2-amino-2-ethoxymethyl-1,3-propanediol hydrochloride1\4H_2O mp 78-79°, (C,H,Cl,N).

Example AB

4-Aza-3-hydroxymethyl-3-methyl-1-oxaspiro(4,5)decane

A solution of 2-amino-2-methyl-1,3-propanediol (Aldrich, 303.4 g, 3.0 mol), cyclohexanone (Fisher, 294.5 g, 3.0 mol) and $PhCH_3$ (400 mL) was refluxed for approximately 2 h with azeotropic removal of H_2O. The material which crystallized from the $PhCH_3$ on cooling was recrystallized twice from hexane to give 444.4 g of 4-aza-3-hydroxymethyl-3-methyl-1-oxaspiro(4.5)decane (80%) mp 52-54°, (C,H,N).

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4-Aza-3-methoxymethyl-3-methyl-1-oxaspiro(4.5)decane

A mechanically stirred 60% dispersion of NaH in mineral oil (Alfa-Ventron, 75g, 1.9 mol) was washed with dry hexane to remove the oil and suspended in dry DMF (200 mL). To the mixture was added a solution of 4-aza-3-hydroxymethyl-3-methyl-1-oxaspiro(4.5)decane (27.8 g, 1.5 mol) in dry DMF (200 mL) keeping the reaction mixture temperature between 30-35°. Small amounts of DMF were added as necessary to facilitate stirring. The mixture was stirred at RT for 1.5 h, then cooled and treated with methyl iodide (Fisher, 234.2 g, 102.7 mL, 1.65 mol) keeping the reaction temperature between 20-30°. The mixture was stirred 2 h at RT and slowly treated with absolute EtOH (40 mL), then diluted with dry Et_2O (3 L). The reaction mixture was filtered and the solvent removed by rotary evaporation. The residue was then fractionally distilled to give 209.7 g (70.3%) of 4-aza-3-methoxymethyl-3-methyl-1-oxasprio(4.5)decane as a colourless liquid bp 114°/14 mm, (C,H,N).

2-Amino-3-methoxy-2-methyl-1-propanol

A solution of 4-aza-3-methoxymethyl-3-methyl-1-oxaspiro(4.5)decane (299 g, 1.5 mol) and 6 N HCl (500 mL) was refluxed for 60 min. On cooling, two layers formed, the upper one containing cyclohexanone was removed by extraction with Et_2O (2x400 mL). The lower aqueous layer was concentrated on a rotary evaporator to give a syrup which then was treated with excess 50% NaOH. The resulting slurry was extracted with Et_2O/CH_2Cl_2 (2:1, 4x500 mL), then with CH_2Cl_2 (500 mL). The solvent was removed by rotary evaporation to give 198 g of pale oil. Fractional distillation of this oil gave 166g (93%) of 2-amino-3-methoxymethyl-1-propanol as a colourless oil, bp 94°C/17 mm, (C,H,N).

Example AC

1α, 2α, 3α-2-Amino-1,3-cyclohexanediol acetate

This compound was prepared by the method of F. Lichtenthaler (Ber, 96, 851 (1963)), mp 175-177°, (C,H,N), (lit 175-177°, F. Lichtenthaler, Ber. 96, 851 (1963)).

Example AD

2-Isopropyl-2-nitro-1,3-propanediol

A solution of 2-methyl-1-nitropropane (38.7 g, 0.375 mol prepared by the procedure of N. Kornblum, B. Tunbe, and H. Ungnade, J.Am.Chem,Soc., 1954, 76, 3029) and NEt_3 (Eastman 3.79 g, 0.0375 mol) in CH_3OH (50 mL) was added dropwise to 37% aqueous formaldehyde solution (Mallinckrodt 76.2 g, 0.938 mol) at a rate such that the reaction mixture temperature did not exceed 30°. After 72 h, the solution was concentrated under vacuum and the residue was dissolved in H_2O (250 mL). The solution was continuously extracted for 1 h with CH_2Cl_2 (1 L). The CH_2Cl_2 solution was dried ($MgSO_4$), filtered, and concentrated to give 53.3 g of 2-isopropyl-2-nitro-1,3-propanediol a waxy, white solid (87%); mp 67-72°C (lit. mp 87-88°, B.M. Vanderbilt and H.B. Hass, Ind. Eng. Chem. 32, 34 (1940). In our hands this procedure failed to give the desired compound).

2-Amino-2-isopropyl-1,3-propanediol acetate

Using the procedure in example AM, 2-isopropyl-2-nitro-1,3-propanediol gave a 98% yield of 2-amino-2-isopropyl-1,3-propanediol acetate mp 155-155.5°. (H.S. Broadbent et al. J. Heterocyclic Chem., 13, 337 (1975) report the synthesis of this compound as the free base (mp 70-72°)).

Example AE

Ethyl N-benzylidene-L-alaninate

Ethyl N-benzylidene-L-alaninate was prepared according to the general procedure of G. Stork et al., J. Org. Chem. 41, 249 (1976), bp 98-100°/0.4 mm (lit. 100°/0.3 mm, A. Calcayai et al., Synthesis 445 (1981)).

2-(2-Iodoethoxy)tetrahydro-2H-pyran

Freshly distilled dihydropyran (Aldrich, 59.0 g, 0.7 mol) was added dropwise to a cooled solution of iodoethanol (Aldrich, 98 g, 0.57 mol) in Et_2O (1L) containing 0.1 g of p-toluenesulfonic acid (Eastman). The solution was then stirred for 1 h at 5°. Solid K_2CO_3 (Mallinckrodt, 5 g) was then added to the reaction mixture and the

resulting suspension stirred an additional 1 h at RT. The reaction was then filtered and the remaining solid washed with Et_2O (1L). The organic solutions were combined and concentrated on a rotary evaporator (in a flask washed with 1% NEt_3 in H_2O). The crude 2-(2-iodoethoxy)-tetrahydro-2H-pyran (100 g, 68.9%) was used without further purification.

Ethyl 2-benzylideneamino-2-methyl-4-((tetrahydro-2H-pyran-2-yl)-oxy)butyrate

A solution of lithium diisopropylamide was prepared by dropwise addition of n-BuLi (Aldrich 1.6 M in hexane, 228 mL, 0.365 mol) to a solution of diisopropylamine (Aldrich, 51.6 g, 0.51 mol) in a mixture of dry THF (700 mL) and dry HMPA (Aldrich, 40 mL) kept at 30-40°. The solution was then cooled to -70° and a solution of ethyl N-benzylidene-L-alaninate (74.9 g, 0.365 mol) was added dropwise to the solution allowing the reaction mixture to warm to -20° for several min. The resulting red solution was then cooled to -70°.

2-(2-Iodoethoxy)tetrahydro-2H-pyran (98.1 g, 0.383 mol) was then added to the solution at such a rate that the temperature in the reaction mixture did not rise above -65°. The solution was allowed to warm slowly to RT and stirred for 14 h. The volume of the solution was reduced to 300 mL by a stream of dry N_2 during the last few hours to facilitate the final workup. The reaction was quenched with sat. NaCl (800 mL) and diluted with Et_2O (800 mL). The Et_2O was removed and the aqueous layer extracted with hexane (500 mL). The Et_2O and hexane layers were combined and dried (Na_2SO_4). The solution was filtered and the solvent removed to give 124 g of crude red oil. Bulb to bulb distillation (in 1% aq. NEt_3 washed glassware) (210° bath temperature/0.3 mm) gave 95 g of ethyl 2-benzylideneamino-2-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)butyrate which was homogeneous by vpc and gave acceptable NMR and mass spectra. It was stored under N_2 in the refrigerator and was used without further purification.

2-benzylamino-2-methyl-4-((tetrahydropyran-2-yl)oxy)butanol

A solution of ethyl 2-benzylideneamino-2-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)butyrate (100.0 g, 0.3 mol) in THF (100 mL) was added slowly to a suspension of lithium aluminum hydride (Alfa-Ventron, 22.77 g, 0.6 mol) rapidly stirred in dry THF (1L) at such a rate to maintain a gentle reflux. After the addition was

complete the mixture was refluxed for 4 h. The reaction mixture was cooled and treated successively with H_2O (23 mL), 15N NaOH (23 mL) and H_2O (45 mL). The solid was removed by filtration and washed with THF (200 mL). The organic layers were combined and concentrated by rotary evaporation to give 2-benzylamino-2-methyl-4-((tetrahydropyran-2-yl)oxy)butanol (81.1 g, 92.0%) as a thick oil which was used without further purification.

2-Benzylamino-2-methyl-1,4-butanediol

The crude 2-benzylamino-2-methyl-4-((tetrahydropyran-2-yl)oxy)-butanol (80.1 g, 0.273 mol) was dissolved in 3N HCl (128 mL). After 5 min the mixture was washed with Et_2O (200 mL). The aqueous solution was concentrated by rotary evaporation to give a thick oil which was cooled and basified with excess 50% NaOH. The oily amine which formed was extracted with Et_2O (3x200 mL). The Et_2O extracts were combined and concentrated to give 63.6 g of a thick oil. Distillation gave 49.8 g (94%) of 2-benzylamino-2-methyl-1,4-butanediol as a pale yellow oil (bp 168-170°/0.35 mm) (C,H,N).

2-Amino-2-methyl-1,4-butanediol hydrochloride

2-Benzylamino-2-methyl-1,4-butanediol (31.08 g, 0.149 mol) was dissolved in 95% EtOH (240 mL) containing Con HCl (21 mL, 0.25 mol) and 5% Pd/C (10.0 g) and reduced in a Parr apparatus at 40 psi over 37 h at RT. The catalyst was then removed by filtration and the solvent removed by rotary evaporation (bath at 60°) to give 20.91 g of 2-amino-2-methyl-1,4-butanediol hydrochloride (90.2%) as a clear, thick, colourless oil with acceptable NMR and mass spectra. It was used without further purification. This compound has been reported as its acetate salt (G. Cardillo et al., Chem. Comm. 1308, 1982), but no data was given.

Example AF

10-Chloroanthracene-1-carboxylic acid

1-Anthroic acid (24 g, 0.108 mol) was treated with N-chlorosuccinimide (Aldrich, 24 g, 0.18 mol) in N-methylpyrrolidinone (Eastman, 600 mL) and heated under N_2 at 90° of 1.5 h. The reaction mixture was diluted with 3.5 L H_2O filtered, dried, and the precipitate recrystallized from EtOAc to afford 16.41 g (59%) of 10-chloroanthracene-1-carboxylic acid mp 257-277°, (C,H,Cl).

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Ethyl 10-chloroanthracene-1-carboxylate

10-Chloroanthracene-1-carboxylic acid (17.3 g, 0.0674 mol), con H_2SO_4 (1.0 mL), and abs. EtOH (500 mL) was refluxed for 3 days using 4 Å molecular sieves in a Soxhlet extractor to remove H_2O. The solvent was removed and then partitioned between EtOAc and satd. $NaHCO_3$. The solvent was then removed from the organic layer to give 14.86 g (77%) of ethyl 10-chloroanthracene-1-carboxylate, which was used without further purification.

10-Chloro-1-anthracenemethanol

A solution of ethyl 10-chloroanthracene-1-carboxylate (14.86 g, 0.052 mol) in THF (300 mL) was treated with $LiBH_4$ (Alfa-Ventron, 1.14 g, 0.052 mol) and refluxed for 16 h. The reaction mixture was poured into ice water and acidified with HCl to pH2. The solid was filtered, washed with H_2O (500 mL), air dried and then chromatographed on a plug of SiO_2 (500 g) using EtOAc as the eluting solvent. The solvent was removed by rotary evaporation to give a solid, which was crystallized from CCl_4 to give 10.3 g (81%) of 10-chloro-1-anthracenemethanol mp 138-140°, (C,H,Cl).

10-Chloroanthracene-1-carbaldehyde

10-Chloro-1-anthracenemethanol (8.8 g, 0.036 mol) was dissolved in CH_2Cl_2 (200 mL) and treated with $BaMnO_4$ (Aldrich, 15 g, 0.059 mol) for 3 days and briefly brought to reflux. The reaction mixture was filtered, and the filtrate reduced to dryness. The residue was chromatographed by preparative HPLC using $PhCH_3$ as the eluting solvent to give 6.0 g (69%) of slightly impure 10-chloroanthracene-1-carboxaldehyde, which was used without further purification.

Example AG

3-Nitro-2,4-pentanediol

A solution of nitromethane (Aldrich, 73.3 g , 1.2 mol) and acetaldehyde (Eastman, 158.6 g, 3.6 mol) was cooled in a ice bath. H_2O (80 mL) and $Ca(OH)_2$ (0.40 g) were then added to the flask. The mixture was stirred under N_2 for 8 h, neutralized with CO_2 and filtered. The filtrate was extracted continuously with CH_2Cl_2 (1L) for 6 h. The CH_2Cl_2 extract was concentrated under vacuum to give 114.6 g (77%) of

crude 3-nitro-2,4-pentanediol, a pale yellow syrup. This material was unstable and was used without further purification. Z. Eckstein and T. Urbanski, Roczniki Chem. 26, 571 (1952), also report the synthesis and isolation of this product as a crude material.

(2α,4α,5α,6α)-4,6-Dimethyl-5-nitro-2-phenyl-1,3-dioxane

A solution of the crude mixture of 3-nitro-2,4-pentanediols (115 g 0.77 mol) from above, benzaldehyde (Fisher 81.7 g, 0.77 mol) and p-toluenesulfonic acid (Fisher 1.28 g) in benzene (400 mL) was refluxed for 1.5 h with azeotropic removal of H_2O. After removal of the solvent under vacuum, the crude product (a complex mixture) was dissolved in abs. EtOH (150 mL). After 36 h, the crystals that had formed (RT) were collected and dried to give yield 25.8 g, of a 5:1 mixture (based on NMR) of desired product and another isomer (C,H,N). Pure 2α,4α,5α,6α-4,6-dimethyl-5-nitro-2-phenyl-1,3-dioxane was obtained after recrystallization from abs. EtOH mp 117.5-118° (C,H,N).

meso-3-Amino-2,4-pentanediol acetate

Prepared from (2α,4α,5α,6α)-4,6-dimethyl-5-nitro-2-phenyl-1,3-dioxane as described for example AM except that the temperature was 50°C and subsequently recrystallized from 95% EtOH to give meso-3-amino-2,4-pentanediol acetate mp 108.5-109.5°, (C,H,N).

Example AH

12-Ethyl-6-chrysenecarbaldehyde

6-Ethylchrysene (Cambridge Chemical, Inc. 60 g, 0.234 mol) was formylated according to the procedure outlined in example A, except that CH_2Cl_2 (1000 mL) was used as the reaction solvent. The crude material was chromatographed on a plug of SiO_2 (1 kg) using $PhCH_3$ as the eluting solvent, affording 50.38 g (76%) of 12-ethyl-6-chrysenecarbaldehyde mp 138-139°, (C,H).

Example AI

10-(Imidazol-1-yl)-9-anthracenecarbaldehyde

A solution of 10-chloro-9-anthraldehyde (Aldrich, 15 g, 0.062 mol), imidazole (Aldrich, 10.2 g, 0.15 mol) and DMF (300 mL) at 55° was treated with KOtBu (MCB, 7.9 g, 0.07 mol) and stirred for 30 min. The reaction mixture was poured into 0.1M NaOH (1.5 L). The filtered precipitate was chromatographed on a plug of SiO_2 (500 g) using CH_2Cl_2 (3 L) as the initial eluting solvent to remove starting material and by-products. The yellow product band was then eluted with EtOAc (2 L) to yield (after removal of solvent and drying) 12.29 g (73%) of 10-(imidazol-1-yl)-9-anthracenecarbaldehyde mp 194-196°, (C,H,N), (EtOAc).

Example AJ

12-Ethoxychrysene-6-carbaldehyde

6-Ethoxychrysene (Cambridge Chemical. Inc., 48 g, 0.176 mol) was formylated according to the procedure outlined in example A, except that CH_2Cl_2 (1000 mL) was used as the reaction solvent. After isolation, the crude material was chromatographed on a plug of SiO_2 (500 g) using CH_2Cl_2 as the eluting solvent to give after removal of solvent and drying 33.7 g (64%) of 12-ethoxychrysene-6-carbaldehyde mp 173.5-176°, (C,H).

Example AK

4-Chloro-10-(2-hydroxyethoxy)-9-anthracenecarbaldehyde

An isomeric mixture of 1-chloro- and 4-chloro-9-anthraldehydes (36.8 g, 0.133 mol) in ethylene glycol (1000 mL) and THF (200 mL) was treated with KOtBu (MCB, 12.5, 0.11 mol) and heated at 80° for 14 h. The reaction mixture was poured into H_2O (2 L). The precipitate was filtered, washed with H_2O (500 ml) sucked dry, then chromatographed on a plug of silica (500 g) using CH_2Cl_2 as the intial eluting solvent to remove starting material and by-products. The desired product was then eluted with EtOAc to give, after removal of solvent and recrystallization from EtOAc, 3.0 g (7.5%) of 4-chloro-10-(2-hydroxyethoxy)-9-anthracenecarbaldehyde mp 141-145°, (C,H,Cl).

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Example AL

Formylation of 3-ethylfluoranthene

3-Ethylfluoranthene (Cambridge Chemical Inc., 70 g , 0.304 mol) was formylated according to the procedure outlined in 1A, except that CH_2Cl_2 (1 L) was used as the reaction solvent. Chromatography on a plug of SiO_2 (1 kg) yielded three partially purified products, each of which was rigorously purified by preparative HPLC using $PhCH_3$ as the eluting solvent. Each of the three products were isomeric mixtures as described below.

a) 3- and 4-Ethylfluoranthene-7-carbaldehyde, 5.0 g (6%), (Rf=0.55, SiO_2 $PhCH_3$), (C,H).

b) 4-Ethylfluoranthene-3-carbaldehyde and 3-ethylfluoranthene-2-carbaldehyde, 4.7 g (6%), Rf=0.49, SiO_2, $PhCH_3$), (C,H).

c) 3- and 4-Ethylfluoranthene-8-carbaldehyde, 47.3 g (60%), (Rf=0.38, SiO_2, $PhCH_3$), (C,H).

d) 4-Ethylfluoranthene-3-carbaldehyde

The mixture b (4.7 g) was recrystallized twice from CH_2Cl_2/hexane to yield 1.83 g (2% from 3-ethylfluoranthene) of 4-ethylfluoranthene-3-carbaldehyde mp 113.5-116°, (C,H).

Example AM

3-Methyl-3-nitro-2,4-pentanediol

Solid NaOH (Mallinckrodt, 286 mg, 7.15 mmol) was added to a solution of 3-nitro-2-butanol (Aldrich, 59.6 g, 0.50 mol) and acetaldehyde (Eastman 132 g, 1.50 mol) in anhydrous DMSO (MCB, 100 mL). The reaction was stirred under N_2 for 5 days. Glacial acetic acid (0.5 mL) was then added to the solution. The solvent was then removed by rotary evaporation, (45°C bath temperature) to give a yellow liquid. This was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (5x200 mL). The combined CH_2Cl_2 extracts were washed sequentially with H_2O (50 mL) and sat.

NaCl (50 mL), dried ($MgSO_4$) and filtered. Volatile components were removed from the filtrate under vacuum (first at aspirator vacuum and at 0.1 mm (bath temperature of 50-135°)) leaving a viscous yellow liquid (53.0 g, 64%). This was mixed with EtOAc/hexane (1:1) (50 mL) and subjected to flash chromatography on SiO_2 (1.5 kg, Merck silica gel 60 230-400 mesh) using 11 L of EtOAc/hexane (1:1) as the eluting solvent and collecting 500 mL fractions. Appropriate fractions were combined and the solvent removed by rotary evaporation to give a total of 43.5 g (53%) of the diastereomeric mixture of 3-methyl-3-nitro-2,4-pentanediols (two meso forms and a d,l pair, easily distinguished by NMR in DMSO-d^6).

(+-)-(2R*,3RS,4R*)-3-Nitro-3-methyl-2,4-pentanediol and meso-3-Nitro-3-methyl-2,4-pentanediol

The chromatographic process described above gave partial separation of the diastereomers. The early fraction (500 mL) gave 13.1 g of one of the meso-3-nitro-3-methyl-2,4-pentanediols as a colourless solid mp 60-61° (C,H,N). The remaining fractions were combined to give 38.3 g of the isomeric mixture containing both the meso- and d, l-compounds. Recrystallization from EtOAc/hexane (300 mL, 2:1) gave 27.8 g of a 4:1 ratio of (+-)-(2R*,3RS,4R*)-3-nitro-3-methyl-2,4-pentanediol and the other of the meso-3-nitro-3-methyl-2,4-pentanediols mp 79-86° (C,H,N). These two materials were then used without further purification.

(+-)-(2R*,3RS,4R*)-3-Amino-3-methyl-2,4-pentanediol acetate

To a solution of 3-methyl-3-nitro-2,4-pentanediol (16.3 g, 0.1 mol; the 4:1 mixture of d,l pair to one meso form described above) in 95% EtOH (150 mL) was added glacial acetic acid (19 mL) and 10% Pd/C (2.0 g, MCB). The reduction was carried out in a Parr apparatus at 50 psi of H_2 during a 70 h period at RT, the catalyst was removed by filtration through a Millipore (TM) filter and the solvent was removed under vacuum (RT, 2 days). The viscous, colourless syrup was dissolved in abs. EtOH (30 mL). While slightly warm, the solution was made cloudy by adding anhydrous Et_2O (100 mL) and was then placed in a refrigerator. Colourless crystals formed over two days which were filtered, washed with Et_2O and dried in a vacuum oven (at RT). The yield of pure (+-)-(2R*,3RS,4R*)-3-amino-3-methyl-2,4-pentanediol acetate (as shown by NMR in DMSO-d_6) was 12.8 g mp 110.5-112° (C,H,N). USSR patent 521,272 (CA 85: 177498) mentions 3-amino-3-methyl-2,4-pentanediol as an intermediate but no synthetic details, physical properties, or stereochemistry was presented in the abstract.

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meso-3-Amino-3-methyl-2,4-pentanediol acetate

Using the procedure described above meso-3-methyl-3-nitro-2,4-pentanediol-(undetermined configuration) gave meso-3-amino-3-methyl-2,4-pentanediol acetate (53%), mp 137-138°, (C,H,N).

Example AN

(+-) (2R*,3S*)-2-Methyl-2-nitro-1,3-butanediol (A) and
(+-) (2R*,3R*)-2-Methyl-2-nitro-1,3-butanediol (B)

To a mixture of 2-nitro-1-propanol (Aldrich, 63.0 g, 0.60 mol) and acetaldehyde (Eastman, 39.6 g, 0.90 mol) cooled in an ice bath under N_2 was added cold H_2O (40 mL) and calcium hydroxide (200 mg). The mixture was allowed to warm to RT over 2 h and then stirred for 68 h. The resulting solution was neutralized with excess solid CO_2. The mixture was stirred for 1 h before filtration through a Millipore (TM) filter. The filtrate was then concentrated under vacuum at 35°. The residue, a viscous syrup which partially crystallized on drying under vacuum (0.1 mm, RT, 48 h), was triturated with cold Et_2O (35 mL). Solid white crystals which formed were collected by filtration, washed with cold Et_2O (3 x 15 mL) and dried under vacuum (0.1 mm, RT) to give 34.1 g of material, judged by NMR to be diastereomer A (purity >97%, racemic). After recrystallization, the diastereomeric purity was >99%, mp 78.5-81° (lit. 78°; cf. Beil 1, 482 in Henry, Bull.Soc.Chim.Fr.[3] 15, 1224), (C,H,N).

The original filtrate (including wash) was concentrated under vacuum to a pale yellow liquid which was subjected to flash chromatography as follows: The sample was mixed with hexane: EtOAc (2:1, 100 mL) and added to a column of dry silica gel 60 (1500 g, Merck, 230-400 mesh). The column was eluted with hexane:EtOAc (2:1, 12 L) then hexane:EtOAc (1:1, 6 L) while 500 mL fractions were collected. Appropriate fractions were combined. Pure product was found in the final 8 L; yield, 38.7 g of viscous syrup, judged by NMR to be a 1:1 mixture of the two racemic diastereomers (A and B), (C,H,N).

This and another batch of the 1:1 diastereomeric mixture (prepared as described above) were combined (67 g, total) and subjected to successive liquid-liquid partitioning between H_2O and EtOAc to give pure samples (99% on the basis of NMR and HPLC (Hamilton PRP-1 column using 3.5% aqueous acetonitrile as the mobile phase)) of A (24.9 g, k'=4.3, C,H,N) and B (15.8 g, k'=2.1, C,H,N, a colourless, viscous liquid).

(+-)(2R*,4S*,5R*)-4,5-dimethyl-5-nitro-2-phenyl-1,3-dioxane and
(+-)(2R*,4S*,5S*)-4,5-dimethyl-5-nitro-2-phenyl-1,3-dioxane

The relative configurations of the two diastereomeric pairs (A and B) were assigned on the basis of comparative NMR analysis of the respective cyclic acetals derived from benzaldehyde. Thus, A (1.49 g, 0.01 mol) and benzaldehyde (Mallinckrodt, 1.06 g, 0.01 mol) were condensed in benzene in the presence of a catalytic amount of p-toluenesulfonic acid with azeotropic removal of water (according to the method of H. Piotrowska, B. Serafin and T. Urbanski, Tetrahedron 109, 379 (1963)). After successive washing with sat. $NaHCO_3$ solution, drying ($MgSO_4$), filtration, and removal of the benzene by rotary evaporation, a pale yellow solid was obtained. A solution of this product in ethanol at 0^oC provided an oil which was isolated by decanting the mother liquor and drying under vacuum (0.1 mm, RT). The yield was 1.48 g (62%) of (+-) (2R*,4S*,5R*)-4,5-dimethyl-5-nitro-2-phenyl-1,3-dioxane (C,H,N).

Similarly prepared from B and benzaldehyde was (+-) (2R*,4S*,5S*)-4,5-dimethyl-5-nitro-2-phenyl-1,3-dioxane (74%) (C,H,N).

(+-) (2R*,3R*)-2-Amino-2-methyl-1,3-butanediol acetate

Prepared from (+-) (2R*,3R*)-2-methyl-2-nitro-1,3-butanediol as described for example AM (97%) (C,H,N) mp 117-121°.

(+-) (2R*,3S*)-2-Amino-2-methyl-1,3-butanediol acetate

Prepared from (+-) (2R*,3S*)-2-methyl-2-nitro-1,3-butanediol as described for AM (93%) (C,H,N) mp 163-165°C.

(+-) (2R*,3R*)-2-Amino-2-methyl-1,3-butanediol acetate

Prepared from (+-) (2R*,3R*)-2-methyl-2-nitro-1,3-butanediol as described for example AM (97%) (C,H,N) mp 117-121°.

(+-) (2R*,3S*)-2-Amino-2-methyl-1,3-butanediol acetate

Prepared from (+-) (2R*,3S*)-2-methyl-2-nitro-1,3-butanediol as described for AM (93%) (C,H,N) mp 163-165°C.

Example 1

B. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol hydrochloride

To a 2 L Erylenmeyer flask was added 6-chrysenecarbaldehyde (21.2 g, 82.7 mmol) from example A, 2-methyl-2-amino-1,3-propanediol (Aldrich, 9.13 g, 86.8 mmol), p-toluenesulfonic acid. H_2O (Eastman, 0.5 g, 2.5 mmol), and 500 mL of toluene. The mixture was warmed to reflux for a few minutes and H_2O (2-3 mL) was driven off. The resulting golden coloured solution was allowed to cool room temperature, diluted with 500 mL of absolute EtOH and stirred overnight. $NaBH_3CN$ (Aldrich, 95%, 2.51 g, 42 mmol) was added to the reaction. After it was dissolved, a indicator (bromocresol green, Eastman, 5 mg) was added. To the resulting blue solution was added 5 drops of 1M g-HCl in absolute EtOH every 15 minutes. After 3 days the indicator turned green then yellow and voluminous white precipitate was present in the flask. To the flask was then added 10 mL of 1M g-HCl in absolute EtOH. The reaction was diluted to 4 with absolute ether and stirred for 1 hour. The precipitate was then filtered through a medium porosity glass fritted funnel and pressed dry. The filter cake was washed thoroughly with 5x250 mL portions of 20% HCl, pressed dry and then washed with 4x500 mL portions of CH_2Cl_2, pressed and sucked dry. The solid was dissolved in 1400 mL of absolute EtOH. 1 mL of 1M g-HCl in absolute EtOH and 5 g of Calgon (Trade Mark) brand of activated charcoal were added and the mixture boiled and filtered through a pad of Celite (Trade Mark of John Manville Co.) brand of filter-aid. The clear yellow solution was concentrated to 500 mL and diluted to 2 with absolute Et_2O.

Further crystallisation (2x) from CH_3OH/Et_2O mixtures (1/3) gave 18.07 g (57.2%) mp = 241-243° (dec) of 2-((6-chrysenylmethyl)amino)-2-methyl-1,3-propanediol hydrochloride.

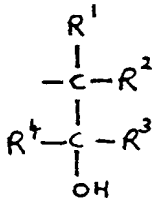
Examples 2 - 49

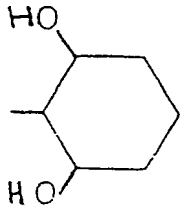
Using methods analogous to that described in Example 1 and utilising the appropriate aldehyde and aminoalkanol starting materials, the following compounds of formula (I) were prepared in the form of their hydrochloride salts (all compounds analysed correctly for the assigned structures):

Compound	Ar	R^1	R^2	R.Solv.	M.P.°
2	10-Cl-9-An	Ch_2OH	CH_3	M/EE	268-269(d)
3	9-An	CH_2OH	CH_3	M/EE	139-140(d)
4	10-SMe-9-An	CH_2OH	CH_3	E/EE	225-226(d)
5	10-(2-CH_2CH_2Cl)-9-An	CH_2OH	CH_3	E/EE	229-231(d)
6	4,10-Cl-9-An	CH_2OH	CH_3	E/EE	261-262(d)
7 1/4H_2O	10-CH_2OH-9-An	CH_2OH	CH_3	E/EE	209-210(d)
8 1/2H2O	10-Me-9-An	CH_2OH	CH_3	E/EE	>300(d)
9	10-Br-9-An	CH_2OH	CH_2	M/EE	263-264(d)
10	10-Cl-9-An	CH_2OH	C_2H_5	M/EE	252-254
11	4,5-Cl-9-An	CH_2OH	CH_3	E/EE	239.5-240.5(d)
12	3-Fl	CH_2OH	CH_3	M/EE	262-265.5(d)
13	4-Cl-9-An	CH_2OH	CH_3	E/EE	225-226(d)
14	10-$SOCH_3$-9-An	CH_2OH	CH_3	E/EE	266-268(d)
15	2-Tr	CH_2OH	CH_3	E/EE	207-208.5(d)
16	10-OMe-9-An	CH_2OH	CH_3	E/EE	173-174(d)
17	10-CN-9-An	CH_2OH	CH_3	M/EE	307-308
18	10-Br-1-An	CH_2OH	CH_3	E/EE	225-226.5(d)
19	1-An	CH_2OH	CH_3	E/EE	189-191(d)
20a	2-Cl-9-An	CH_2OH	CH_3	M/EE	265-266(d)
b	3-Cl-9-An	CH_2OH	CH_3	M/EE	268-269(d)
21	2-SEt-9-An	CH_2OH	CH_3	E/EE	201-202(d)
22	2-SCH_2CH_2OH-9-An	CH_2OH	CH_3	E/EE	199-200(d)
23	10-Cl-9-An	CH_2OH	CH_2OH	E/EE	251-254(d)
24	3,10-Cl-9-An	CH_2OH	CH_3	M/EE	303-304(d)
25	2,10-Cl-9-An	CH_2OH	CH_3	M/EE	305-306(d)
26	6-Ch	CH_2OH	CH_2OH	M/EE	238-239(d)
27	6-Ch	CH_2OH	C_2H_5	E/EE	241-243(d)
28	3-Fl	CH_2OH	CH_2OH	M/EE	240-241(d)
29	3-Fl	CH_2OH	C_2H_5	M/EE	250-252(d)
30	10-OEt-9-An	CH_2OH	CH_3	E/EE	229-230(d)

31	7-Fl	CH_2OH	CH_3	M/EE	204-206(d)
32 $1/2H_2O$	10-CH_2CHOH-9An	CH_2OH	CH_3	E/EE	179-181(d)
33	10-SO_2CH_3-9-An	CH_2-OH	CH_3	M/EE	238-239(d)
34	3-Cl-9-An	CH_2OH	CH_3	M/EE	268-289(d)
35	2-Et-9-An	CH_2OH	CH_3	E/EE	203-205(d)
	3-Et-9-An	CH_2OH	CH_3	E/EE	
*36	6-Ch	CH_2OH	CH_2OEt	M/EE	230-232(d)
37	6-Ch	CH_2OCH_3	CH_3	E/EE	233-234(d)
38	3-Fl	CH_2OCH_3	CH_3	E/EE	222-223(d)
*39 9/20	3-Fl	CH_2OH	CH_2OEt	E/EE	179-180
*40	9-An	CH_2OH	CH_2OEt	E/EE	176.5-178.5
*41	6-Ch	CH_2OH	CH_2OEt	M/EE	280-282(d)
*42	3-Fl			M/EE	258-260(d)
**43 $1/3H_2O$	6-Ch	CH_2OH	i-Pr	E/EE	223-223.5(d)
**44	3-Fl	CH_2OH	i-Pr	E/EE	216-217(d)
*45 1/3 EtOH	6-Ch	CH_2CH_2OH	CH_3	E/EE	233-235(d)
*46 $11/20H_2O$	3-Fl	CH_2CH_2OH	CH_3	E/EE	210-212(d)
47 $1/4H_2O$	10-$CH_2CH_2OCH_3$-9-An	CH_2OH	CH_3	E/EE 183(d)	182-
48 $11/20\ H_2O$	10-Im-9-An	CH_2OH	CH_3	E/EE	212-215(d)
49	9-An	CH_2OCH_3	CH_3	E/EE	214-215(d)

In all compounds,
$R^3 = R^4 = H$

In examples 41 and 42,  represents a cyclohexanediol ring.



Key: An = anthracenyl
Fl = fluoranthenyl
Tr = triphenylenyl
Ch = chrysenyl
R.Solv = recrystallisation solvent
Im = imidazol-yl
M.P. = melting point
Et = ethyl
i-Pr = iso-propyl
M/EE = methanol/diethyl ether
E/EE = ethanol/diethyl ether
(d) = decomposed.

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* In these instances the aminoalkanol starting material was in the form of a hydrochloride salt which was neutralised with an equimolar amount of methanolic sodium methoxide and, after warming, the solvent was removed by rotary evaporation before the reductive amination was carried out as described in example 1.

** In these instances the aminoalkanol starting material was in the form of an acetate which was reacted with an equimolar amount of sodium methoxide in methanol and, after warming, the solvent was removed by rotary evaporation before the reductive amination was carried out as described in example 1.

Example 50

A. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate

To a 12 L round bottomed flask equipped with overhead stirrer, condenser, thermometer, and Dean-Stark trap was addded chrysene-6-carbaldehyde (Cambridge Chemical Inc., 202 E. Smith St., Milwaukee, WI, 53207, 260 g, 1.01 mol), 2-amino-2-methyl-1,3-propanediol (Aldrich, 213 g, 2.03 mol), p-toluenesulfonic acid monohydrate (Aldrich, 20.8 g, 0.104 mol) and 3.8 L of $PhCH_3$. The mixture was stirred at reflux with removal of H_2O for 2 h (or until no further H_2O was collected). The mixture was cooled to RT and diluted with 3.8 L of absolute EtOH. Solid sodium borohydride (MCB, 46 g, 1.22 mol) was added in portions to the stirred mixture with the temperature maintained at 25-30° by external cooling. After the addition was completed, the reaction was stirred an additional 3 h at RT. The reaction mixture was then concentrated under vacuum to a volume of 800 mL keeping the flask temperature at 40° or less. The slurry was diluted with H_2O (6 L) and cooled to 5°.

The solid was removed by filtration and washed with H_2O (2x1.5 L).* The solid was then suspended in a mixture of SD3A (US Industrial Chem. Co., 2.5 L) and methanesulfonic acid (Alfa Ventron, 107.2 g, 1.12 mol). The resulting solution was filtered and diluted with 5 L of $PhCH_3$. After crystallization overnight at RT the mixture was cooled at 5° for 1 h and filtered. The solid was washed with $PhCH_3$ (100 mL) and dried to give 417 g (93%) (after a second crop obtained from the filtrate was added) of 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate mp 239-240° (dec), (C,H,N,S).

B. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol

To a rapidly stirred solution of 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol hydrochloride from example 1 (20 g, 52.36 mmol) in a mixture of CH_3OH) (200 mL) ahd H_2O (800 mL) was added dropwise over 10 min a 1M NaOH solution (55 mL). The resulting white precipitate was filtered and washed with warm H_2O (4x500 mL) and then with Et_2O (1 L), sucked dry and placed in a vacuum oven overnight. A total of 17.43 g (96.4%) of 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol mp 200-202°, (C,H,N) was obtained.

C. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol lactate

A mixture of 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol free base (50B) (3.45 g, 10 mmol) and lactic acid (Fisher, 85% liquid, 1.04 g, 10 mmol) in CH_3OH (500 mL) was brought to reflux and filtered through a glass fritted funnel. The solvent was removed by rotary evaporation to give a crude white solid. This was crystallized (CH_3OH/Et_2O) 3 times to give 1.84g (42.2%) of 2-((6-chrysenylmethyl)amino)-2-methyl-1,3-propanediol lactate mp 163-164°, (C,H,N).

D. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol citrate

A mixture of 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol free base (50B) (3.45 g, 10 mmol) and citric acid (Sigma, 1.92 , 10 mmol) in CH_3OH (500 mL) was warmed until it dissolved then filtered through a glass fritted funnel. The solvent was then removed to give a crude white solid. This was boiled with abs. EtOH (2x300 mL) and filtered to give a white solid. This was then recrystallized 2x (CH_3OH/Et_2O) filtered and dried overnight in a vacuum oven to give 1.24 g of 2-((6-Chrysenylmethyl)amino)-2- methyl-1,3-propanediol citrate mp 146-151°, (C,H,N).

E. 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol-hydroxyethanesulfonate

2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol methanesulfonate (10.0 g, 26.63 mmol) was neutralized with 1N NaOH (30 mL) in CH_3OH/H_2O (200/800 mL) as in procedure 1D. The white solid which formed was filtered, washed successively with warm H_2O (3x500 mL), CH_3OH (200 mL), and Et_2O (2x500 mL), sucked semidry and then resuspended in CH_3OH (500 mL). To this was added a 0.43 aqueous solution of 2-hydroxyethanesulfonic acid (30 mL). Slight warming gave a solution which was then filtered. The

* Note: In the subsequent procedures referring to this method, the particular example was suspended in either abs. EtOH or CH_3OH then methanesulfonic acid was added. After slight warming and filtration, the resulting solution was diluted with Et_2O, hexane, or $PhCH_3$. The precipitate which formed then was filtered and then recrystallized to give the desired compound.

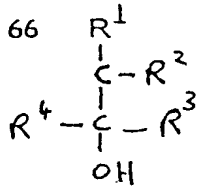
solvent was removed by rotary evaporation to give a wet white solid. This was triturated with dry Et_2O to give 2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol 2-hydroxyethanesulfonate, (C,H,N,S).

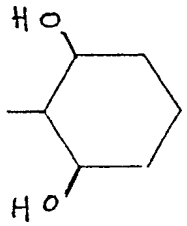
Examples 51 - 66

Using methods analogous to that described in example 50A, the following compounds of formula (I) were prepared in the form of their methanesulfonate salts (all compounds analysed correctly for the assigned structures):

Compound	Ar	R^1	R^2	R.Solv.	M.P.°
51	10-Cl-9-An	CH_2OH	CH_3	M/EE	234-235(d)
52	10-SMe-9-An	Ch_2OH	CH_3	E/EE	193-194(d)
53	10-(2-CH_2CH_2Cl)-9-An	CH_2OH	CH_3	E/EE	210-210.5(d)
54	4,5-Cl-9-An	CH_2OH	CH_3	M/EE	252-253(d)
55	4-Cl-9-An	CH_2OH	CH_3	M/EE	223-233.5(d)
56	2-Tr	CH_2OH	CH_3	M/EE	259-261(d)
57 3/4H_2O	10-morpholino-9-An	CH_2OH	CH_3	E/EE	159-160(d)
58	12-Et-6-Ch	CH_2OH	CH_3	E/EE	189-192(d)
59 1/3H_2O	12-Cl-6-CH	CH_2OH	CH_3	E/EE	233-233.5(d)
60	12-OC_2H_5-6-Ch	CH_2OH	CH_3	E/EE	202-204(d)
61 1/3H_2O 1/10 i-PrOH	4-Cl-10-(2-OCH_2CH_2OH)-9-An	CH_2OH	CH_3	P/EE	156-158(d)
62	4-Et-3-Fl	CH_2OH	CH_3	E/hex	198-199(d)
*63	6-Ch	Ch_2OH	H	M/EE	208-209(d)
*64	9-An	CH_2OH	iPr	E/EE	192-194(d)
65	9-An	$CH_2CH_2OHCH_3$		E/EE	212-213(d)
66	9-An	see below	M/EE	251-252(d)	

* Key as for examples 2 to 49 with the addition that P/EE refers to an isopropanol/tirthyl ether solvent mixture and E/hex refers to an ethanol/hexane solvent mixture. In example 66 R^1 represents a cyclohexanediol-ring





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In these instances the aminoalkanol starting material was in the form of a hydrochloride salt which was neutralised with an equimolar amount of methanolic sodium methoxide and, after warming, the solvent was removed by rotary evaporation before the reductive amination was carried out as described in example 1.

Example 67

2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediyl diacetate

A mixture of 2-((6-chrysenylmethyl)amino)-2-methyl-1,3-propanediol hydrochloride (5.0 g, 13.1 mmol) and acetylchloride (Aldrich, 5.0 mL, 70.3 mmol) were refluxed in dry THF (200 mL) under N_2 for 12 h. The reaction mixture was poured into saturated $NaHCO_3$ (500 mL) and extracted with EtOAc (3x500 mL). The EtOAc layers were combined, dried (K_2CO_3) and filtered to give a slightly yellow clear liquid. The solvent was removed to give an off-white solid. This was recrystallized 3x from $PhCH_3$/hexane (1:1). After filtration and drying, 3.67 g (65.2%) of 2-((6-chrysenylmethyl)amino)-2-methyl-1,3-propanediyl diacetate was obtained mp 136-137.5°, (C,H,N).

Example 68

Meso-3-((6-Chrysenylmethyl)amino)-2,4-pentanediol methanesulfonate

To a round-bottomed flask was added meso-3-amino-3-methyl-2,4-pentanediol acetate (57C) and an equimolar amount of sodium methoxide (MCB) and CH_3OH (100 mL). After warming to aid solution, the solvent was removed by rotary evaporation, and after addition of chrysene-6-carbaldehyde the reaction run following the normal reductive amination procedure outlined in example 50A to give meso-3-(((6-chrysenylmethyl)amino)-2,4-pentanediol methanesulfonate mp 221-223), (CH_3OH/Et_2O), (C,H,N,S).

Examples 69 and 70

2-β-((3-Fluoranthenylmethyl)amino)-1-α,3-α-cyclohexanediol methanesulfonate and 2-β-((6-Chrysenylmethyl)amino)-1-α,3-α-cyclohexanediol methanesulfonate

Using the procedure in example 50B, compound 42 was converted to its free base. Addition of an equivalent of methanesulfonic acid (Alfa-Ventron 99.5%) followed by recrystallization (EtOH/Et_2O) gave 2-β-((3-fluoranthenylmethyl)amino)-1-α,3-α-cyclohexanediol methanesulfonate, mp 214-216° (d), (C,H,N,S). 2-β-((6-chrysenylmethyl)amino-1-α,3-α-cyclohexanediol methanesulphonate, mp 280-281° (d), C,H,N,S) was prepared from the corresponding hydrochloride in similar manner.

Example 71

(+-)-(2R*,3RS,4R*)3-((6-Chrysenylmethyl)amino)-3-methyl-2,5-pentanediol methanesulfonate

To a round-bottomed flask was added (+-)-(2R*,3RS,4R*)3-amino-3-methyl-2,4-pentanediol acetate and an equimolar amount of sodium methoxide (MCB) and CH_3OH (100 mL). The solvent was then removed by rotary evaporation and after addition of chrysene-6-carbaldehyde, the reaction run following the normal reductive amination procedure outlined in example 1 to give (+-)-(2R*,3RS,4R*)3-((6-Chrysenylmethyl)amino)-3-methyl-2,5-pentanediol methanesulfonate mp 182-183° (dec). (EtOH/Et_2O), (C,H,N,S).

Example 72

(+-) (2R*,3S*)-2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-butanediolhydrochloride 1/3H_2O

To a round-bottomed flask was added (+-)-(R*,S*)-2-amino-2-methyl-1,3-butanediol acetate and an equimolar amount of sodium methoxide (MCB) and CH_3OH (100 mL). After warming, the solvent was removed by rotary evaporation, and after addition of chrysene-6-carbaldehyde the reaction run following the normal reductive amination procedure outlined in example 1 to give (+-)(2R*,3S*)-2-((6-chrysenylmethyl)amino)-2-methyl-1,3-butanediol hydrochloride. 1/3 H_2O mp 238-239° (dec), (EtOH Et_2O), (C,H,Cl,N).

Example 73

(+-) (2R*,3S*)-2-((9-Anthracenylmethyl)amino)-2-methyl-1,3-butanediolhydrochloride H_2O

Following the procedure outlined for example 73 anthracene-9-carbaldehyde (Aldrich) and (+-)-(R*,S*)-2-amino-2-methyl-1,3-butanediol acetate gave (+-) (2R*,3S*)-2-((9-Anthracenylmethyl)amino)-2-methyl-1,3-butanediol hydrochloride H_2O mp 216-217° (dec), ($EtOH/Et_2O$), (C,H,Cl,N).

Example 74

(+-)-(2R*,3R*)-2-((6-Chrysenyl)methyl)amino)-2-methyl-1,3-butanediolhydrochloride

Using the procedure outlined for example 73 chrysene-6-carbaldehyde and (+-) (2R*,3R*)-2-amino-2-methyl-1,3-butanediol acetate (40E) gave (+-)-(2R*,3R*)-2-((6-Chrysenyl)methyl)amino)-2-methyl-1,3-butanediol hydrochloride, mp 236-237.5° (dec), (CH_3OH/Et_2O), (C,H,Cl,N).

Example 75

(+-)-(2R*,2S*)-2-(((3-fluoranthenyl)methyl)amino)-2-methyl-1,3-butanediol hydrochloride

Using the procedure outlined for example 73, fluoranthene-3-carbaldehyde and (+-)(2R*,3S*)-2-amino-2-methyl-1,3-butanediol acetate gave (+-)-(2R*,2S*)-2-(((3-fluoranthenyl)methyl)amino)-2-methyl-1,3-butanediol hydrochloride mp 242-243° (dec), $EtOH/Et_2O$, (C,H,Cl,N).

Example 76

(+-) (2R*,3S*)-2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-butanediol methanesulfonate

Using the reductive amination procedure outlined in example 50A the two intermediates in example 73 gave (+-) (2R*,3S*)-2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-butanediolmethanesulfonate mp 220-221° (dec), ($EtOH/Et_2O$), (C,H,N,S).

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Example 77

Antitumour Test Results for 2-((6-chrysenylmethyl)amino)-2-methyl- 1, 3-propanediol

Methods for evaluating the antitumour activity of these compounds are essentially those used in the Tumour Panel by the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, A.Goldin, et al., Methods in Cancer Research, Vol. XVI, p. 165, Academic Press (1979). Some modifications, in dose level and schedule have been made to increase the testing efficiency.

Lymphocytic Leukemia P388/0 Test

CD2-F_1 mice, of the same sex, weighing within a 3 gram range surrounding 20 g, are used for this test. Control and test animals are injected intraperitoneally with a suspension of 10^6 viable P388/0 tumor cells on day 0. In each test several dose levels which bracket the LD_{20} for the compound are evaluated; each dose level group contains 6 animals. The test compounds are prepared either in physiologic saline containing 0.05% Tween 80 or distilled water containing 5% dextrose and are administered intraperitoneally on days 1,5 and 9 relative to tumour implant. Doses are on a mg/kg basis according to individual animals' body weights. The day of death for each animal is recorded, the median identified for each group and the ratios of median survival time for treated (T)/control (C) groups are calculated. The criterion for activity is T/C x 100 >120%. The results of several tests are summarised in Table I below.

Table I

Compound	Optimal Dosage (mg/kg)	T/C x 100% (Excluding 30 day Survivors)
1	121	+280
3	150	+130
19	77	+204
2	425	+228
9	450	+200
8	94	+160
4	110	+262
5	130	+225
7	165	+170
17	387	+190
14	45	+220
16	120	+220
18	300	+225
6	300	+204
11	300	+204
25	450	+210
24	600	+200
12	90	+270
15	84	+200
13	200	+215
20a	150	+170
21	281	+145

22	440	+145
23	277	+140
32	160	+300

Lymphocytic Leukemia L1210 Test

The protocol for this test is identical with that for P388/0 except that the number of L1210 cells implanted on day 0 is 10^5/mouse. The mouse strain used is CD2-F_1, and the criterion for activity is T/C x 100 >125%. Results of L1210 testing are summarised in Table II below.

Table II

Compound of Example	Optimal Dosage (mg/kg)	T/C x 100% (Excluding 30 Day Survivors)
1	120	+252
4	110	+194
5	150	+217

Malanotic Melanoma B16

B6C3-F_1 mice of the same sex, weighing within a 3 gram range surrounding 20 g, are used for this test. A suspension of B16 cells is prepared from a non-necrotic portion of solid tumour tissue obtained from a passage mouse. One gram of tumour is homogenised in 9 mL ice-cold Earle's salts solution and filtered through 100 mesh screen to remove debris. 0.5 mL of the resulting brei is injected intraperitoneally to each animal. Dosing is carried out as in the P388/0 and L1210 tests. Days of death are recorded for a 60 day period and T/C ration calculated as in the P388/0 and L1210 tests. The results of B16 testing are summarised below in Table III.

Table III

Compound of Example	Optimal Dosage (mg/kg)	T/C x 100% (Excluding 30 Day Survivors)
1	100	+146
4	110	+143
5	130	+146
6	300	+200
14	30	+216

M5076 Sarcoma Test

This sarcoma arose as a solid tumour in the ovary of a C57B1/6 mouse and was subsequently converted to the ascitic form for intraperitoneal use. The protocol for this test is identical with that for P388/0, the B6C3-F_1 mouse strain is used and the criterion for activity is T/C x 100 $\geq$ 125%. Results of M5076 testing are summarized in Table below.

Table. M5076 Screening Data

Compound	Optimal Dose (mg/kg)	T/C x 100%*
1	105	+ 168
12	85	+ 162

* Excluding 30 Day Survivors

Colon 38 Carcinoma Test

This chemically-induced tumour arose in a C57B1/6 mouse and is maintained as a solid tumour in that mouse strain. The subcutaneously growing solid tumour is aseptically excised from passage mice and placed in sterile saline. The tumour is trimmed free of visible necrotic and connective tissue, then divided into 2-3 mm cubes. A cube is implanted subcutaneously in the ventral thoracic region with a sterile trochar on day 0. In each test several dose levels which bracket the LD_{20} for the compound are evaluated. Ten animals are included in each dose level group and 30 in the untreated control group. The test compounds are prepared either in physiolgic saline containing 0.05% Tween 80 or distilled water containing 5% dextrose and are administered intraperitoneally on days 1, 5 and 9 after tumour implant. Doses are on a mg/kg basis according to individual animals' body weights. At day 20 the animals are sacrificed and the longest (L) and the shortest (W) dimensions of each tumour measured with vernier calipers. Tumor weight is 100 calculated from the formula L(W)2/2. The criterion for activity isT/C x < 42%. The results of Colon 38 testing are summarized below.

Compound	Optimal Dose (mg/kg)	T/C x 100%
1	120	36
5	150	38
12	65	23

Lewis Lung Carcinoma Test

This tumour arose spontaneously in the lung of a C57B1/6 mouse and is maintained by subcutaneous passage in the strain. The solid tumour is excised aseptically and placed in sterile saline. Pieces of viable tumour tissue are minced finely with scissors and forced through a 200 mesh stainless steel screen to disaggregate the tumour cells into a suspension. 10^6 viable cells are injected intravenously into the tail vein of BD-F, mice of the same sex weighing 20 ± 3 grams. In each test several dose levels which bracket the LD_{20} for the compound are evaluated. Ten animals are included in each dose level group and 20 in the untreated control group. The test compounds are prepared and administered as in the P388/0 protocol. The day of death for each animal is recorded, the median identified for each group and the ratios of median survival time for treated (T)/control (C) groups are calculated. The criterion for activity is T/C x 100 $\geq$ 140%. The results of Lewis lung testing are summarized in Table below.

Compound	Optimal Dosage (mg/kg)	T/C x 100%
1	105	+191
12	85	+222

Example 78 : Herpes simples 1/vero Test

Antiviral testing against Herpes simplex 1/vero was done using plaque inhibition methods as outlined in P. Collins and D. J. Bauer, Proc. N.Y. Acad. Sci. 284, 49 (1977) and by plaque reduction methods as outlined in P. Collins and D.J. Bauer, J. Antimicrobial Chemotherapy 3, Supplement A, 73 (1977). The column headings labelled Score, Toxicity, and Zone of Inhibition refer to the plaque inhibition screen while the IC_{50} heading to the plaque reduction screen.

Table Results of Antiviral Screening Against herpes simplex 1/vero

Compound No.	Score [A]	Toxicity	IC_{50} [B]
2	-4	Y	1.60
3	-3		
24	-4	Y	
4Z	-4	Y	12
48	-2	Y	23.8

A. Score : 0 = no inhibition, -1 = 1.25% inhibition, -2 = 26-50% inhibition
-3 = 51-75% inhibition, -4 = 76-100% inhibition

Example 79 : Candida albicans Test

Antifungal testing against Candida albicans (CN 1863) was done with slight modifications using a combination of broth and agar dilution assays as outlined in Laboratory Handbook

of Medical Mycology, Chapter 6, pages 441-446, M.R. McGinnis, Academic Press, New York, NY, 1980.

Table Results of Antifungal Testing Against Candida albicans (CN 1863)

Compound No.	MIC (mg/L)
2	>50
3	>50
1	100
12	30

Medium : Wellcotest sensitivity test agar plus 7% lysed horse blood

Example 80

Antibacterial Screening

Antibacterial testing against Mycoplasma smegmatis (S3264) and Streptococcus pyogenes (CN10) was done with slight modifications using standard agar dilution assays as outlined in Manual of Clinical Microbiology Second Ed., E.H. Lenette, E.H. Spaulding and J.P. Truant Eds., American Society for Microbiology, Washington, DC,1974.

Table Results of Antibacterial Testing Against Streptococcus pyogenes (CN10)

Compound No.	MIC (mg/L)
1	>10

Example 81 : Mycoplasma smegmatis Test

Results of Antibacterial Screening Against Mycoplasma smegmatis (53264)

Compound No.	MIC (mg/L)
3	<5
1	<10
58	10

Example 82 : Trichomonas vaginalis Test

Antiprotozoal testing against Trichomonas vaginalis was done using methods outlined by R.M. Michaels in Advances in Chemotherapy 3, 39-108(1968).

Table Results of Antiprotozoal Testing Against Trichomonas vaginalis (in vitro)

Compound No. (mg/L)	Dose	Result[A]
8	40	.4
7	40	.4

(Stenton or Modified Diamond's medium)

A. Screen Code 0 = no inhibition, -1 = 1-25% inhibition, -2 = 26-50% inhibition, -3 = 51-75% inhibition,

-4 = 76-100% inhibition.

Example 83 : Nippostrongylus brasiliensis Test

Anthelmintic testing against Nippostrongylus brasiliensis was done using methods outlined in D.C. Jenkins, R. Armitage, and T. S. Carrington, Zeitschrift for Parasitenkunde 63, 261-269 (1980)

Table

Results of Anthelmintic Screening Against Nippostrongylus brasiliensis (Immature - free living stages)

Compound of Example No.	MIC (mg/L)
8	50
3	>50
2	>50

Example 84 : Eimeria tenella Testing

Antiprotozoal testing against Eimeria tenella was done using methods outlines in V.S. Latter and D. Wilson, Parasitology 79, 169 (1979)

Table XIII : Results of Antiprotozoa Screening Against Eimeria tenella (in vitro)

Compound of Example No.	Dose (mg/L)	Result[A]
12	0.31	.4
3	1.25	.4

A. Screen Code 0 = no inhibition, -1=25% inhibition, -2= 26-50% inhibition, -3=51-75%

inhibition, -4=76-100% inhibition

Example 85 : LD_{50} Tests

Table : LD_{50} Values for Selected Compounds

(IP single dose - CD - 1 Male Mouse)

Compound No.	LD_{50} (mk/kg)
12	82
1	140
4	100
3	160
2	250
32	110

Example 86: Formulation Examples

A. TABLET

Compound of Formula I (as hydrochloride)	500.0 mg
Pregelatinised Corn Starch	60.0 mg
Sodium Starch Glycolate	36.0 mg
Magnesium Stearate	4.0 mg

The Compound of formula (I) is finely ground and intimately mixed with the powdered excipients, pregelatinised corn starch and sodium starch glycolate. The powders are wetted with purified water to form granules. The granules are dried and mixed with the magnesium stearate. The formulation is then compressed into tablets weighing approximately 600 mg each.

B. TABLET

Compound of formula (I)	500.0 mg
Corn Starch	70.0 mg
Lactose	83.8 mg
Magnesium Stearate	4.2 mg
Polyvinylpyrrolidone	14.0 mg
Stearic Acid	28.0 mg

The Compound of formula (I) is finely ground and intimately mixed with the powdered excipients, corn starch and lactose. The powders are wetted with a solution of polyvinylpyrrolidone dissolved in purified water and denatured alcohol to form granules. The granules are dried and mixed with the powdered stearic acid and magnesium stearate. The formulation is then compressed into tablets weighing approximately 700 mg each.

C. CAPSULES

Compound of formula (I)	500.0 mg
Corn Starch	50.0 mg
Magnesium Stearate	3.0 mg

The finely divided Compound of formula (I) is mixed with powdered corn starch and wetted with denatured alcohol to densify the powder. The dried powder is mixed with stearic acid and filled into hard-shell gelatin capsules.

D. SYRUP

Compound of formula (I)		250.0 mg
Ethanol		250.0 mg
Glycerin		500.0 mg
Sucrose		3,500.0 mg
Flavouring Agent		q.s.
Colouring Agent		q.s.
Preserving Agent		0.1%
Purified Water	q.s. to	5.0 ml

The Compound of formula (I) is dissolved in the ethanol, glycerin, and a portion of the purified water. The sucrose and preserving agent are dissolved in another portion of hot purified water, and then the colouring agent is added and dissolved. The two solutions are mixed and cooled before the flavouring agent is added. Purified water is added to final volume. The resulting syrup is throughly mixed.

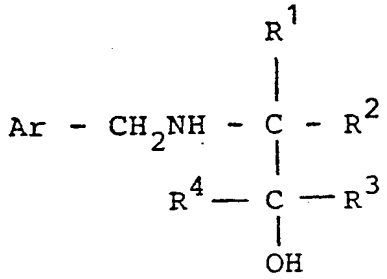
E. IV INJECTION

Compound of formula (I)	5.0 mg
Glycerin	q.s. for isotonicity
Preservative	0.1%
Hydrochloric Acid or	as needed for
Sodium Hydroxide	pH adjustment
Water for Injection	q.s. to 1 ml

The compound of formula (I) and preservative is added to the glycerin and a portion of the water for injection. The pH is adjusted with hydrochloric acid or sodium hydroxide. Water for injection is added to final volume and solution is complete after thorough mixing. The solution is sterilised by filtration through a 0.22 micrometer membrane filter and aseptically filled into sterile 10 ml ampoules or vials.

Claims

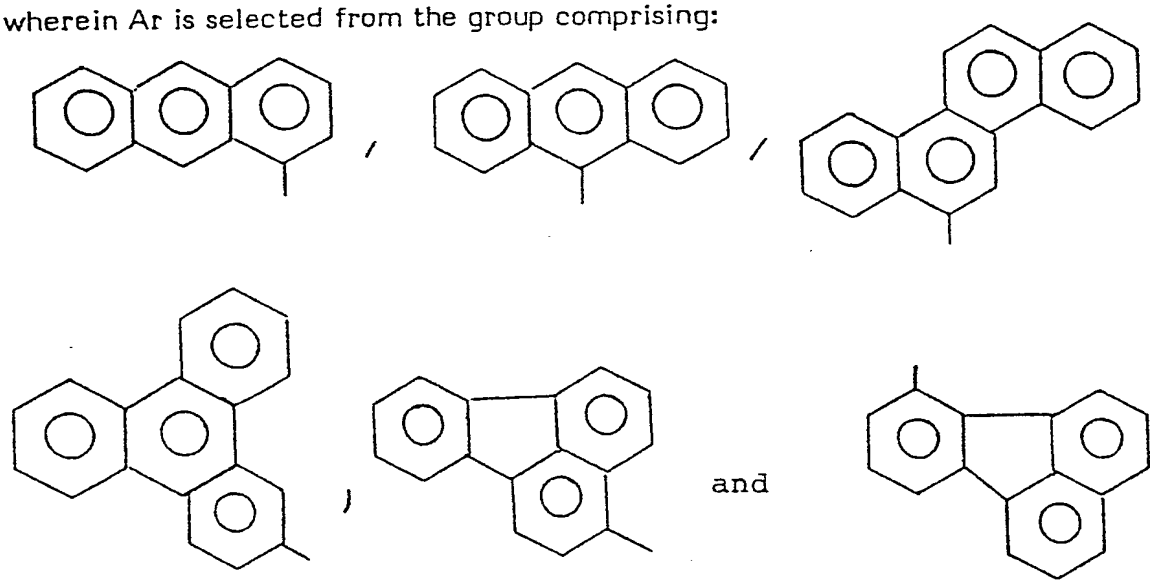
1. A compound of the formula (I):



(I)

or a monomethyl or monoethyl ether thereof, the compound of formula (I) including its ethers containing not more than 28 carbon atoms in total, or an ester of salt thereof;

wherein Ar is selected from the group comprising:

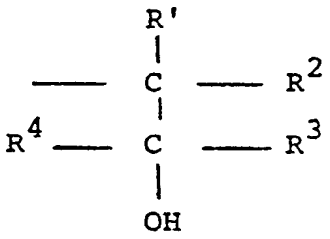


optionally substituted by one or two substituents which taken together contain not more than four carbon atoms in total and which are the same or different and are selected from halo; cyano; C_{1-3}alkyl or C_{1-3}alkoxy each optionally substituted by hydroxy or C_{1-2}alkoxy; halo substituted C_{1-2}alkyl or C_{1-2}alkoxy; a group $S(O)_nR^5$ wherein n is an integer 0,1 or 2 and R^5 is C_{1-2} alkyl optionally substituted by hydroxy or C_{1-2} alkoxy; or Ar is optionally substituted by a group NR^6R^7 containing not more than 5 carbon atoms wherein R^6 and R^7 are the same or different and each is a C_{1-3} alkyl group or NR^6R^7 forms a five or six membered heterocyclic ring optionally containing one or two additional hetero atoms;

R^1 is C_{1-3} alkyl substituted by hydroxy;

R^2 is hydrogen, C_{1-3} alkyl or hydroxymethyl;

R^3 and R^4 are the same or different and each is hydrogen, methyl or ethyl;
R^1, R^2, R^3 and R^4 taken together containing not more than five carbon atoms;
or the group:



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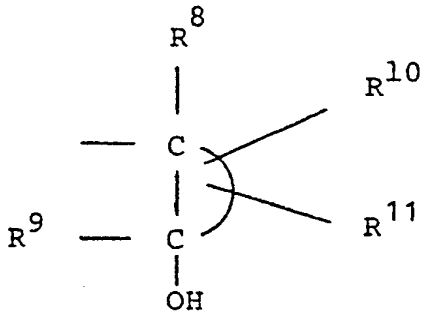
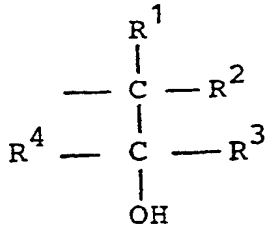


wherein -C-C- is a five or six membered saturated carbocyclic ring containing two or three hydroxy groups;
R^8 is hydrogen, methyl or hydroxymethyl;
R^9 and R^{10} are the same or different and each is hydrogen or methyl;
R^{11} is hydrogen, hydroxy, methyl or hydroxymethyl;
R^8, R^9, R^{10}, R^{11} and the -C-C- ring taken together containing less than seven carbon atoms.

2. A compound according to claim 1 wherein Ar is 6-chrysenyl, 7-fluoranthenyl or substituted 1- or 9- anthracenyl.

3. A compound according to either claim 1 or 2 wherein Ar is substituted by C_{1-2} alkyl or C_{1-2} alkoxyl each optionally substituted by chloro, hydroxy or methoxy; or a group $S(O)_nR^5$ or chloro, imidazolyl, morpholino, cyano or bromo. Preferred substitutents are chloro, 2-chloroethyl or $OCH_2CH_2R^{12}$ wherein R^{12} is hydrogen, hydroxy or methoxy or a group $S(O)_nCH_3$ wherein n is the integer 0, 1 or 2.

4. A compound according to any one of claims 1 to 3 in which



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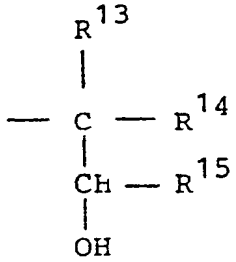
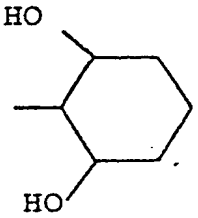
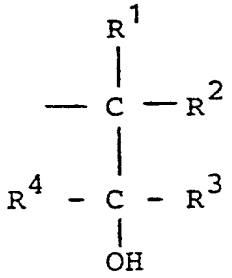


or



wherein R^{13} is CH_2OH, $CH(CH_3)OH$ or CH_2CH_2OH;
R^{14} is hydrogen, C_{1-3}alkyl, or CH_2OH;
R^{15} is hydrogen or methyl.

5. A compound according to any one of claims 1 to 4 in which



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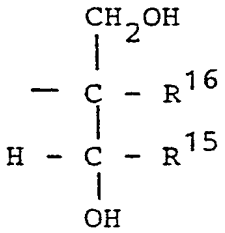

wherein R^{15} is hydrogen or methyl and R^{16} is hydrogen, methyl or ethyl.

6. A compound of the formula (I) according to claim 1 selected from the group comprising:

2-((6-Chrysenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((9-Anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((1-Anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Chloro-9-anthracenylmethyl)-amino)-2-methyl-1,3-propanediol,

2-((10-Bromo-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-Methyl-2-((10-methyl-9-anthracenylmethyl)amino)-1,3-propanediol,

2-Methyl-2-((10-methylthio-9-anthracenylmethyl)amino)-1,3-propanediol,

2-((10-(2-Chloroethyl)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Hydroxymethyl)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

10-((1,1-Bis)hydroxymethyl)ethylamino)methyl-9-anthracene-carbonitrile,

2-Methyl-2-((10-methylsulfinyl-9-anthracenylmethyl)amino)-1,3-propanediol,

2-((10-Methoxy-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Bromo-1-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((4,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((4,5-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((2,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((3,10-Dichloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((3-Fluoranthrylmethyl)amino)-2-methyl-1,3-propanediol,

2-Methyl-2-((2-triphenylenylmethyl)amino)-1,3-propanediol,

2-((4-Chloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,
2-((2-Chloro-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Ethylthio-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-(2-Hydroxyethylthio)-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-Chloro-9-anthracenylmethyl)amino)-2-hydroxymethyl-1,3-propanediol,

2-((7-Fluoranthenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((10-(2-Hydroxyethyloxy)-9-anthracenylmethyl)amino-2-methyl-1,3-propanediol,

2-((10-Ethoxy-9-anthracenylmethyl)amino)-2-methyl-1,3-propanediol,

2-((6-Chrysenylmethyl)amino)-2-hydroxymethyl-1,3-propanediol,

2-((6-Chrysenylmethyl)amino)-2-ethyl-1,3-propanediol,

2-Hydroxymethyl-2-((3-fluoranthenylmethyl)amino)-1,3-propanediol,

2-Ethyl-2-((3-fluoranthenylmethyl)amino-1,3-propanediol,

2-((10-chloro-9-anthracenylmethyl)amino)-2-ethyl-1,3-propanediol

2-((3-chloro-9-anthracenylmethyl)amino-2-methyl-1,3-propanediol,

(+-) (2R*, 3S*)-2-((6-chrysenylmethyl)amino)-2-methyl-1,3-butanediol,

2-((2-ethyl-9-anthracenlymethyl)amino)-2-methyl-1,3-propanediol and
2-((3-ethyl-9-anthracenlymethyl)amino)-2-methyl-1,3-propanediol,

(+-) (2R*, 3S*)-2-((9-anthracenylmethyl)amino)-2-methyl-1,3-butanediol,

(+-) (2R*, 3R*)-2-(((6-chrysenyl)methyl)amino)-2-methyl-1,3-butanediol,

2-(((6-chrysenyl)methyl)amino)-2-ethoxymethyl-1,3-propanediol,

3-methoxy-2-(((6-chrysenyl)methyl)amino)-2-methyl-1-propanol,

3-methoxy-2(((3-fluoranthenyl)methyl)amino)-2-methyl-1-propanol,

(+-) (2R*, 2S*)-2-(((3-fluoranthenyl)methyl)amino)-2-methyl-1,3-butanediol,

2-ethoxymethyl-2-(((3-fluoranthenyl)methyl)amino)-1,3-propanediol,

2-(((9-anthracenyl)methyl)amino)-2-ethoxymethyl-1,3-propanediol,

2-β-((6-chrysenylmethyl)amino)-1-α,3-α-cyclohexanediol

2-β-((3-fluoranthenylmethyl)amino)-1-α,3-α-cyclohexanediol

2-((6-chrysenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((3-fluoranthrenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((6-chrysenylmethyl)amino)-2-methyl-1,4-butanediol

2-((3-fluoranthenylmethyl)amino)-2-methyl-1,4-butanediol

2-(((10-chloro-1-anthracenyl)methyl)amino)-3-methyl-2,5-pentanediol

2-(((10-chloro-1-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

Meso-3-((6-chrysenylmethyl)amino)-2,4-pentanediol

2-((6-chrysenylmethyl)amino)-1,3-propanediol

2-(((12-ethyl-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

2-(((10-(2-methoxyethoxy)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

2-methyl-2-(((10-morpholino-9-anthracenyl)methyl)amino)-1,3-propanediol

2-((9-anthracenylmethyl)amino)-3-methoxy-2-methyl-1-propanol

2-(((12-chloro-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

2-((9-anthracenylmethyl)amino)-2-isopropyl-1,3-propanediol

2-((9-anthracenylmethyl)amino)-2-methyl-1,4-butanediol

2-(((10-(1H-imidazol-1-yl)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

2-(4-ethyl-3-fluoranthenyl)methyl)amino)-2-methyl-,3-propanediol

2-(((12-ethoxy-6-chrysenyl)methyl)amino)-2-methyl-1,3-propanediol

(1α, 2β, 3α)-2-(9-anthracenylmethyl)amino-1,3-cyclohexanediol

2-(((4-chloro-10-hydroxyethoxy)-9-anthracenyl)methyl)amino)-2-methyl-1,3-propanediol

(+-) ($2R^+$,/RS^+, $4R^+$)-3-(6-chrysenylmethyl)amino)-3-methyl-2,5-pentanediol,

2-methyl-2-(((10-methylsulphonyl-1-9-anthracenyl)methyl)amino)-1,3-propanediol

and salts and esters thereof.

7. 2-((6-chrysenylmethyl)amino)2--2-methyl-1,3-propanediol or a salt or ester thereof.

8. Hydrochloride, methanesulfonate, ethanesulfonate, lactate, citrate or isethionate salt of a compound of the formula (I) according to any of claims 1 to 8.

9. A pharmaceutical formulation comprising a compound of the formula (I) or an ether, ester or salt thereof according to any one of claims 1 to 8together with a pharmaceutically acceptable carrier therefor.

10. A pharmaceutical composition according to claim 11, that comprises a sterile aqueous solution of a pharmaceutically and pharmacologically acceptable acid addition salt of a compound of the formula (I) according to any one of claims 1 to 6, that is isotonic with the blood of the recipient.

11. A method for the preparation of a pharmaceutical formulation which comprises bringing into association a compound of formula (I) or an ether, ester or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

12. A novel chemical intermediate utilised in a process according to claims 1 to 9 herein.

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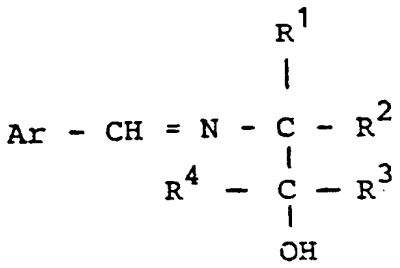
A method for the preparation of a compound of the formula (I) according to any one of claims 1 to 7, which comprises:

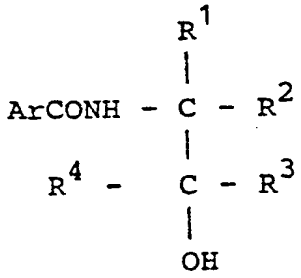
(i) the reduction of a compound of formula (II):



(II)

wherein R^1 to R^4 are as hereinbefore defined, or an appropriately protected derivative thereof, followed by deprotection where appropriate;

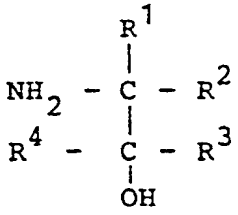
(ii) the reduction of a compound of the formula (V):



(V)

wherein R^1 to R^4 are as hereinbefore defined and the hydroxy groups are optionally protected, followed by deprotection of the hydroxy groups where appropriate, or

(iii) the reaction of a compound Ar CH_2 L, wherein Ar is as hereinbefore defined and L is a leaving group, with a compound of the formula (IV):



wherein R^1 to R^4 are as hereinbefore defined.

4. A novel chemical intermediate of the formula (II), (IV), (V) as hereinbefore defined or of the formula $ArCH_2CHO$ wherein Ar is as hereinbefore defined.